

Original citation:

Scott, R. A., Freitag, D. F., Li, L., Chu, A. Y., Surendran, P., Young, R., Grarup, N., Stancakova, A., Chen, Y., Varga, T. V. et al.. (2016) A genomic approach to therapeutic target validation identifies a glucose-lowering GLP1R variant protective for coronary heart disease. *Science Translational Medicine*, 8 (341). 341ra76.

Permanent WRAP URL:

<http://wrap.warwick.ac.uk/85334>

Copyright and reuse:

The Warwick Research Archive Portal (WRAP) makes this work by researchers of the University of Warwick available open access under the following conditions. Copyright © and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable the material made available in WRAP has been checked for eligibility before being made available.

Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge. Provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

Publisher's statement:

<http://dx.doi.org/10.1126/scitranslmed.aad3744>

A note on versions:

The version presented here may differ from the published version or, version of record, if you wish to cite this item you are advised to consult the publisher's version. Please see the 'permanent WRAP URL' above for details on accessing the published version and note that access may require a subscription.

For more information, please contact the WRAP Team at: wrap@warwick.ac.uk

Genomic approach to therapeutic target validation identifies a glucose-lowering *GLP1R* variant protective for coronary heart disease

All authors with their affiliations appear at the end of this paper.

Author list

Robert A. Scott,^{1‡} Daniel F. Freitag,^{2,3‡} Li Li,^{4‡§} Audrey Y. Chu,⁵ Praveen Surendran,² Robin Young,² Niels Grarup,⁶ Alena Stancáková,⁷ Yuning Chen,⁸ Tibor V. Varga,⁹ Hanieh Yaghootkar,¹⁰ Jian'an Luan,¹ Jing Hua Zhao,¹ Sara M. Willems,^{1,11} Jennifer Wessel,^{12,13} Shuai Wang,⁸ Nisa Maruthur,^{14,15,16} Kyriaki Michailidou,¹⁷ Ailith Pirie,¹⁷ Sven J. van der Lee,¹⁸ Christopher Gillson,¹ Ali Amin Al Olama,¹⁷ Philippe Amouyel,¹⁹ Larraitz Arriola,^{20,21,22} Dominique Arveiler,²³ Iciar Aviles-Olmos,²⁴ Beverley Balkau,^{25,26} Aurelio Barricarte,^{27,22} Inês Barroso,^{3,28} Sara Benlloch Garcia,¹⁷ Joshua C. Bis,²⁹ Stefan Blankenberg,³⁰ Michael Boehnke,³¹ Heiner Boeing,³² Eric Boerwinkle,^{33,34} Ingrid B. Borecki,³⁵ Jette Bork-Jensen,⁶ Sarah Bowden,³⁶ Carlos Caldas,³⁷ Muriel Caslake,³⁸ The CVD50 consortium, L. Adrienne Cupples,^{8,39} Carlos Cruchaga,⁴⁰ Jacek Czajkowski,⁴¹ Marcel den Hoed,⁴² Janet A. Dunn,⁴³ Helena M. Earl,⁴⁴ Georg B. Ehret,⁴⁵ Ele Ferrannini,⁴⁶ Jean Ferrieres,⁴⁷ Thomas Foltynie,²⁴ Ian Ford,³⁸ Nita G. Forouhi,¹ Francesco Gianfagna,^{48,49} Carlos Gonzalez,⁵⁰ Sara Grioni,⁵¹ Louise Hiller,⁴³ Jan-Håkan Jansson,^{52,53} Marit E. Jørgensen,^{54,55} J. Wouter Jukema,⁵⁶ Rudolf Kaaks,⁵⁷ Frank Kee,⁵⁸ Nicola D. Kerrison,¹ Timothy J. Key,⁵⁹ Jukka Kontto,⁶⁰ Zsófia Kote-Jarai,⁶¹ Aldi T. Kraja,⁴¹ Kari Kuulasmaa,⁶⁰ Johanna Kuusisto,^{62,63} Allan Linneberg,^{64,65,66} Chunyu Liu,⁶⁷ Gaëlle Marenne,³ Karen L. Mohlke,⁶⁸ Andrew P. Morris,^{69,70} Kenneth Muir,^{71,72} Martina Müller-Nurasyid,^{73,74,75} Patricia B. Munroe,⁷⁶ Carmen Navarro,^{77,22} Sune F. Nielsen,⁷⁸ Peter M. Nilsson,⁷⁹ Børge G. Nordestgaard,⁷⁸ Chris J. Packard,³⁸ Domenico Palli,⁸⁰ Salvatore Panico,⁸¹ Gina M. Peloso,^{82,83,84} Markus Perola,^{85,60} Annette Peters,^{86,75} Christopher J. Poole,^{87,72} J. Ramón Quirós,⁸⁸ Olov Rolandsson,⁸⁹ Carlotta Sacerdote,^{90,91,92} Veikko Salomaa,⁶⁰ María-José Sánchez,^{93,22} Naveed Sattar,³⁸ Stephen J. Sharp,¹ Rebecca Sims,⁹⁴ Nadia Slimani,⁹⁵ Jennifer A. Smith,⁹⁶ Deborah J. Thompson,¹⁷ Stella Trompet,⁵⁶ Rosario Tumino,⁹⁷ Daphne L. van der A,⁹⁸ Yvonne T. van der Schouw,⁹⁹ Jarmo Virtamo,⁶⁰ Mark Walker,¹⁰⁰ Klaudia Walter,³ GERAD_EC Consortium,[†] Neurology working group Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), Alzheimer's Disease Genetics Consortium,[†] Pancreatic Cancer Cohort Consortium, EPIC-CVD, EPIC-InterAct, Jean E. Abraham,¹⁰¹ Laufey T. Amundadottir,¹⁰² Jennifer L. Aponte,¹⁰³ Adam S. Butterworth,² Josée Dupuis,⁸ Douglas F. Easton,^{17,101} Rosalind A. Eeles,^{61,104} Jeanette Erdmann,¹⁰⁵ Paul W. Franks,^{9,53,106} Timothy M. Frayling,¹⁰ Torben Hansen,⁶ Joanna M. M. Howson,² Torben Jørgensen,^{107,108,109} Jaspal Kooner,^{110,111,112} Markku Laakso,¹¹³ Claudia Langenberg,¹ Mark I. McCarthy,^{114,70} James S. Pankow,¹¹⁵ Oluf Pedersen,⁶ Elio Riboli,¹¹⁶ Jerome I. Rotter,¹¹⁷ Danish Saleheen,¹¹⁸ Nilesh J. Samani,^{119,120} Heribert Schunkert,^{75,121} Peter Vollenweider,¹²² Stephen O'Rahilly,^{28,123,124} CHARGE consortium, The CHD Exome+ consortium, CARDIOGRAM Exome consortium, Panos Deloukas,¹²⁵ John Danesh,^{2,3} Mark O. Goodarzi,¹²⁶ Sekar Kathiresan,^{127,128,83} James B. Meigs,^{129,130} Margaret G. Ehm,¹⁰³ Nicholas J. Wareham,¹ Dawn M. Waterworth¹³¹

¹Medical Research Council Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, UK.

²Department of Public Health and Primary Care, Strangeways Research Laboratory, University of Cambridge, Cambridge, UK.

³The Wellcome Trust Sanger Institute, Cambridge, UK.

⁴Statistical Genetics, Projects, Clinical Platforms & Sciences, GlaxoSmithKline, Research Triangle Park, NC, USA.

⁵Division of Preventive Medicine, Brigham and Women's Hospital, Boston MA, USA.

⁶The Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

⁷Institute of Clinical Medicine, Internal Medicine, University of Eastern Finland, Kuopio, Finland.

⁸Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA.

⁹Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University, Malmö, Sweden.

¹⁰Genetics of Complex Traits, University of Exeter Medical School, University of Exeter, Exeter, UK.

¹¹Genetic Epidemiology Unit, Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands.

¹²Fairbanks School of Public Health, Department of Epidemiology, Indianapolis, IN, US.

¹³Indiana University School of Medicine, Department of Medicine, Indianapolis, IN, USA.

¹⁴Division of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

¹⁵Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University, Baltimore, Maryland.

¹⁶Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland.

¹⁷Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Laboratory, Worts Causeway, Cambridge, UK.

¹⁸Department of Epidemiology, Erasmus University Medical Center, Rotterdam, Netherlands.

¹⁹University of Lille, Institut national de la santé et de la recherche médicale (Inserm), Centre Hospitalier Régional Universitaire de Lille, Institut Pasteur de Lille, UMR1167 - RID-AGE, F-59000 Lille, France.

²⁰Public Health Division of Gipuzkoa, San Sebastian, Spain.

²¹Instituto BIO-Donostia, Basque Government, San Sebastian, Spain.

²²CIBER Epidemiología y Salud Pública (CIBERESP), Spain.

- ²³Department of Epidemiology and Public Health (EA3430), University of Strasbourg, Strasbourg, France.
- ²⁴Sobell Department of Motor Neuroscience, UCL Institute of Neurology, London, UK.
- ²⁵Inserm, Centre de recherche en épidémiologie et santé des populations (CESP), Villejuif, France.
- ²⁶Univ Paris-Sud, Villejuif, France.
- ²⁷Navarre Public Health Institute (ISPN), Pamplona, Spain.
- ²⁸University of Cambridge Metabolic Research Laboratories, Wellcome Trust-MRC Institute of Metabolic Science, Cambridge, UK.
- ²⁹Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA.
- ³⁰Department of General and Interventional Cardiology, University Heart Center Hamburg, Germany.
- ³¹Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, MI, USA.
- ³²German Institute of Human Nutrition, Potsdam-Rehbruecke, Germany.
- ³³Human Genetics Center, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, USA.
- ³⁴Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA.
- ³⁵Department of Genetics, Division of Statistical Genomics, Washington University School of Medicine, St. Louis, MO, USA.
- ³⁶Cancer Research UK Clinical Trials Unit, Institute for Cancer Studies, The University of Birmingham, Edgbaston, Birmingham, UK.
- ³⁷Cancer Research UK Cambridge Institute and Department of Oncology, Li Ka Shing Centre, University of Cambridge, Cambridge, UK.
- ³⁸University of Glasgow, Glasgow, UK.
- ³⁹National Heart, Lung, and Blood Institute (NHLBI) Framingham Heart Study, Framingham, MA, USA.
- ⁴⁰Dep. of Psychiatry, Washington University, School of Medicine, St. Louis, MO, US.
- ⁴¹Division of Statistical Genomics, Department of Genetics and Center for Genome Sciences and Systems Biology, Washington University School of Medicine, St. Louis, MO, USA.
- ⁴²Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden.
- ⁴³Warwick Clinical Trials Unit, University of Warwick, Gibbet Hill Road, Coventry, UK.

⁴⁴University of Cambridge and National Institute of Health Research Cambridge Biomedical Research Centre at Cambridge University Hospitals National Health Service Foundation Trust, Cambridge, UK.

⁴⁵McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University, Baltimore, MD, USA.

⁴⁶Consiglio Nazionale delle Ricerche (CNR) Institute of Clinical Physiology, Pisa, Italy.

⁴⁷Department of Epidemiology, UMR 1027- INSERM, Centre Hospitalier Universitaire (CHU) de Toulouse, Toulouse, France.

⁴⁸Department of Clinical and Experimental Medicine, Research Centre in Epidemiology and Preventive Medicine, University of Insubria, Varese, Italy.

⁴⁹Department of Epidemiology and Prevention, Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Neurologico Mediterraneo Neuromed, Pozzilli, Italy.

⁵⁰Catalan Institute of Oncology (ICO), Barcelona, Spain.

⁵¹Epidemiology and Prevention Unit, Milan, Italy.

⁵²Research Unit, Skellefteå, Sweden.

⁵³Department of Public Health & Clinical Medicine, Umeå University, Umeå, Sweden.

⁵⁴Steno Diabetes Center, Gentofte, Denmark.

⁵⁵National Institute of Public Health, Southern Denmark University, Denmark.

⁵⁶Leiden University Medical Center, Leiden, Netherlands.

⁵⁷German Cancer Research Centre (DKFZ), Heidelberg, Germany.

⁵⁸UK Clinical Research Collaboration (UKCRC) Centre of Excellence for Public Health, Queens University Belfast, Northern Ireland, UK.

⁵⁹University of Oxford, UK.

⁶⁰National Institute for Health and Welfare, Helsinki, Finland.

⁶¹The Institute of Cancer Research, London, UK.

⁶²Institute of Clinical Medicine, Internal Medicine, University of Eastern Finland, Kuopio, Finland.

⁶³Kuopio University Hospital, Kuopio, Finland.

⁶⁴Research Centre for Prevention and Health, Capital region, Copenhagen, Denmark.

⁶⁵Department of Clinical Experimental Research, Rigshospitalet, Glostrup, Denmark.

⁶⁶Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

⁶⁷Framingham Heart Study, Population Sciences Branch, NHLBI/NIH, Bethesda, MD, USA.

- ⁶⁸Department of Genetics, University of North Carolina, Chapel Hill, NC, USA.
- ⁶⁹Department of Biostatistics, University of Liverpool, Liverpool, UK.
- ⁷⁰Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK.
- ⁷¹The University of Manchester, Centre for Epidemiology, Institute of Population Health, Oxford Road, Manchester, UK.
- ⁷²University of Warwick, Coventry, UK.
- ⁷³Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany.
- ⁷⁴Department of Medicine I, Ludwig-Maximilians-University Munich, Munich, Germany.
- ⁷⁵DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany.
- ⁷⁶Clinical Pharmacology, William Harvey Research Institute, Barts and The London, Queen Mary University of London, London, UK.
- ⁷⁷Department of Epidemiology, Murcia Regional Health Council-IMIB Arrixaca, Murcia, Spain.
- ⁷⁸Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark.
- ⁷⁹Lund University, Malmö, Sweden.
- ⁸⁰Cancer Research and Prevention Institute (ISPO), Florence, Italy.
- ⁸¹Dipartimento di Medicina Clinica e Chirurgia, Federico II University, Naples, Italy.
- ⁸²Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA.
- ⁸³Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA.
- ⁸⁴Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA.
- ⁸⁵Institute of Molecular Medicine Finland (FIMM), University of Helsinki.
- ⁸⁶Institute of Epidemiology II, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany.
- ⁸⁷Department of Medical Oncology, Arden Cancer Centre, University Hospital Coventry and Warwickshire.
- ⁸⁸Public Health Directorate, Asturias, Spain.
- ⁸⁹Umeå University, Umeå, Sweden.
- ⁹⁰Unit of Cancer Epidemiology, Citta' della Salute e della Scienza Hospital-University of Turin.

- ⁹¹Center for Cancer Prevention (CPO), Torino, Italy.
- ⁹²Human Genetics Foundation (HuGeF), Torino, Italy.
- ⁹³Escuela Andaluza de Salud Pública, Instituto de Investigación Biosanitaria ibs.GRANADA. Hospitales Universitarios de Granada/Universidad de Granada, Granada, Spain.
- ⁹⁴Institute of Psychological Medicine and Clinical Neuroscience, MRC Centre, Cardiff University, UK.
- ⁹⁵International Agency for Research on Cancer, Lyon, France.
- ⁹⁶Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI, USA.
- ⁹⁷Cancer Registry and Histopathology Unit, "Civic M.P.Arezzo" Hospital, ASP Ragusa (Italy).
- ⁹⁸National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands.
- ⁹⁹University Medical Center Utrecht, Utrecht, The Netherlands.
- ¹⁰⁰Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK.
- ¹⁰¹Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Strangeways Laboratory, Worts Causeway, Cambridge, UK.
- ¹⁰²Laboratory of Translational Genomics, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.
- ¹⁰³Genetics, PCPS, GlaxoSmithKline, RTP, NC, USA.
- ¹⁰⁴Royal Marsden NHS Foundation Trust, Fulham and Sutton, London and Surrey, UK.
- ¹⁰⁵Institut für Integrative und Experimentelle Genomik, Universität zu Lübeck, Lübeck, Germany.
- ¹⁰⁶Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, MA, USA.
- ¹⁰⁷Research Centre for Prevention and Health, Capital region, Denmark.
- ¹⁰⁸Department of Public Health, Institute of Health Science, University of Copenhagen, Denmark.
- ¹⁰⁹Faculty of Medicine, Aalborg University, Denmark.
- ¹¹⁰National Heart and Lung Institute, Imperial College London, London, UK.
- ¹¹¹Imperial College Healthcare NHS Trust, London, UK.
- ¹¹²Ealing Hospital NHS Trust, Middlesex, UK.
- ¹¹³Department of Medicine, University of Kuopio, Kuopio, Finland.
- ¹¹⁴Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM), University of Oxford, UK.
- ¹¹⁵Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA.

¹¹⁶School of Public Health, Imperial College London, UK.

¹¹⁷Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute at Harbor- University of California, Los Angeles (UCLA) Medical Center, Torrance, CA, USA.

¹¹⁸Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, USA.

¹¹⁹Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, UK.

¹²⁰National Institute for Health Research (NIHR) Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester, UK.

¹²¹Deutsches Herzzentrum München, Technische Universität München, Munich, Germany.

¹²²Department of Internal Medicine, BH10-462, Internal Medicine, Lausanne University Hospital (CHUV), Lausanne, Switzerland.

¹²³MRC Metabolic Diseases Unit, Cambridge, UK.

¹²⁴National Institute of Health Research Cambridge Biomedical Research Centre, Cambridge, UK.

¹²⁵William Harvey Research Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University of London, UK.

¹²⁶Division of Endocrinology, Diabetes and Metabolism, Cedars-Sinai Medical Center, Los Angeles, CA, USA.

¹²⁷Broad Institute of Harvard and MIT, Cambridge, Massachusetts, USA.

¹²⁸Cardiology Division, Center for Human Genetic Research, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA.

¹²⁹Division of General Internal Medicine, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA.

¹³⁰Department of Medicine, Harvard Medical School, Boston, MA, USA.

¹³¹Genetics, Projects, Clinical Platforms & Sciences, GlaxoSmithKline, Philadelphia, PA, USA.

‡ These authors contributed equally to the work

† Data used in the preparation of this article were obtained from the Genetic and Environmental Risk for Alzheimer's Disease_Exome Chip (GERAD_EC) Consortium and Alzheimer's Disease Genetics Consortium (ADGC). As such, the investigators within the GERAD_EC Consortium and ADGC contributed to the design and implementation of GERAD_EC and ADGC and/or provided data but did not participate in analysis or writing of this report.

§ Current affiliation: PAREXEL, Durham, NC

*Correspondence can be addressed to:

Dawn.M.Waterworth@gsk.com (D. M. W.); robert.scott@mrc-epid.cam.ac.uk (R. A. S.);
nick.wareham@mrc-epid.cam.ac.uk (N. J. W.)

One Sentence Summary: A missense variant in *GLP1R* associated with lower fasting glucose levels and protective against T2D is associated with lower risk of coronary heart disease, suggesting that GLP1R agonists are not associated with an unacceptable increase in cardiovascular risk.

Abstract

Regulatory authorities have indicated that new drugs to treat type 2 diabetes (T2D) should not be associated with an unacceptable increase in cardiovascular risk. Human genetics may be able to inform development of antidiabetic therapies by predicting cardiovascular and other health endpoints. We therefore investigated the association of variants in 6 genes that encode drug targets for obesity or T2D with a range of metabolic traits in up to 11,806 individuals by targeted exome sequencing, and follow-up in 39,979 individuals by targeted genotyping, with additional *in silico* follow up in consortia. We used these data to first compare associations of variants in genes encoding drug targets with the effects of pharmacological manipulation of those targets in clinical trials. We then tested the association those variants with disease outcomes, including coronary heart disease, to predict cardiovascular safety of these agents. A low-frequency missense variant (Ala316Thr;rs10305492) in the gene encoding glucagon-like peptide-1 receptor (*GLP1R*), the target of GLP1R agonists, was associated with lower fasting glucose and lower T2D risk, consistent with GLP1R agonist therapies. The minor allele was also associated with protection against heart disease, thus providing evidence that GLP1R agonists are not likely to be associated with an unacceptable increase in cardiovascular risk. Our results provide an encouraging signal that these agents may be associated with benefit, a question currently being addressed in randomised controlled trials. Genetic variants associated with metabolic traits and multiple disease outcomes can be used to validate therapeutic targets at an early stage in the drug development process.

Introduction

In 2008, the US Food and Drug Administration issued guidance for industry on new therapies to treat type 2 diabetes (T2D), recommending that sponsors should demonstrate that these treatments are “not associated with an unacceptable increase in cardiovascular risk” (1). This mandate challenges drug developers to prove safety during clinical trials, which is an expensive and late-phase strategy for the identification of such concerns. Instead, genetic approaches may aid in the identification of possible drug side-effects much earlier in the drug development process. Genetic variants can inform the treatment and prevention of human disease (2, 3), either reducing the prioritisation of potential targets (4, 5) or implicating new targets (6, 7). Functional exonic variants can be useful surrogates for

drug effects, when, for example, a loss-of-function (LoF) variant may be a useful tool to understand the consequences of pharmacological inhibition of a particular target protein (7). Recent sequencing efforts have identified a large number of potentially functional low-frequency and rare exonic variants in human populations, even among genes under purifying selection (8–12). Although such variants may influence susceptibility to disease, the high cost of these sequencing approaches has previously meant that they have not been performed in the sample sizes required to allow routine investigation of their association with complex disease and related traits.

A recent targeted exome sequencing study of 202 genes encoding potential drug targets identified an abundance of potentially functional exonic variants (8). Among these 202 genes, six genes encoding drug targets licensed or in development by GlaxoSmithKline (GSK) for treatment of obesity and/or T2D were included. Recognizing that these data could be used to test for genetic variants mimicking pharmacological manipulation of the encoded protein (drug target), we investigated six genes encoding targets of relevance to obesity and T2D. These variants could then serve as tools to aid the broader evaluation of drug-related risk for adverse events mediated via on-target effects.

As a proof of concept for use of genetic variants to evaluate the cardiovascular safety of anti-diabetic agents, we evaluated the widely used glucose-lowering glucagon-like peptide-1 receptor (GLP1R) agonists (13). These agents are long-acting mimetics of the incretin hormone GLP1, which increases insulin secretion after oral consumption of glucose but not after glucose administered intravenously. There are uncertainties over the role of these agents in the aetiology of rare, adverse pancreatic events that have been reported following their usage (14). These therapies have been associated with weight loss (15) and reduced cardiovascular risk factors, and while a recent trial reported non-inferiority of GLP1R-agonists in cardiovascular safety(16), multiple trials evaluating cardiovascular safety have not yet been completed (17). We used a genetic variant in *GLP1R* that is associated with variation in fasting glucose levels and with T2D risk (18) to evaluate the cardiovascular safety of GLP1R agonists. The low-frequency variant protective for T2D was also

protective for coronary heart disease (CHD). These findings support the notion that GLP1R agonists will not confer an increased cardiovascular risk in people. This study also demonstrates how genetic target validation approaches can be employed early in the drug development process to evaluate efficacy and safety.

Results

Association of genetic variants in genes encoding T2D and obesity drug targets

The study design consisted of initial discovery of variants with suggestive associations, to targeted genotyping and *in silico* follow-up analyses (Fig. 1). We investigated the association of 121 variants in six genes encoding therapeutic targets in use or in development for T2D or obesity (*CNR2*, *DPP4*, *GLP1R*, *SLC5A1*, *HTR2C*, *MCHR1*)—drawn from a recent targeted exome sequencing study of 202 genes encoding drug targets (8)—with variation in the following traits: T2D, obesity, body-mass index (BMI), waist circumference, fasting glucose, fasting insulin, and 2-h glucose (Fig. 1). In the “Discovery Analysis”, we identified seven variants potentially associated with T2D- or obesity-related traits (where $p < 0.001$, or which were in a target of interest to GSK and $p < 0.05$) (Table 1). For these seven variants, “Follow-Up Analysis” was performed by targeted genotyping in up to 39,979 additional individuals of European ancestry. Where possible, *in silico* follow-up analysis was performed for traits and variants available in large-scale genetic consortia data.

Initial discovery analyses included 1331 tests of association, with the threshold specified to reach significance in combined analyses being $p < 3.8 \times 10^{-5}$. In a combined analysis of results from the different phases, we identified a low-frequency (~1% minor allele frequency (MAF)) missense variant Ala316Thr; rs10305492 in the *GLP1R* gene to be associated with fasting glucose (Fig. 2A). The variant was in Hardy-Weinberg equilibrium in all genotyped samples ($p > 0.2$). The effect size (i.e. the difference per allele) of 0.09 mM was larger than most common variants previously reported for fasting glucose (Fig. 2B), and was recently found to be associated with fasting glucose in non-overlapping samples from large-scale analyses of coding variant associations with glycaemic traits

(18). The combined analysis of the six other variants in Table 1 did not show evidence of association ($p > 3.8 \times 10^{-5}$, by linear or logistic regression) with the suggestively associated trait in the discovery analysis (“Follow-up” p -values > 0.05 ; “Combined” p -values ≥ 0.005 ; Table 1).

The *GLP1R* gene encodes the GLP1 receptor, the target for GLP-1, a hormone that mediates the augmented response to insulin secretion following oral glucose administration. This receptor is the target for the GLP1R-agonist class of T2D therapeutics and the association of this variant with fasting glucose mimicked a major effect of this class of agents. To further corroborate the utility of this variant as a surrogate indicator of pharmacological modulation of the receptor, we investigated its association with T2D and found that the minor allele was associated with lower risk of T2D [odds ratio (OR) = 0.83 [0.76, 0.91]; $P = 9.4 \times 10^{-5}$; in a fixed effect meta-analysis of log-odds ratios from studies and consortia listed in table S1 and in Supplementary Materials “Studies contributing to follow-up analyses of type-2 diabetes and obesity related traits”; $n_{\text{cases}} = 25,868$, $n_{\text{controls}} = 122,393$]. However, we saw no association of this *GLP1R* variant (Ala316Thr; rs10305492) with fasting insulin, nor with 2-h glucose (Fig. 2A).

Although there were no individuals carrying putative LoF variants in *GLP1R* in the targeted sequencing study, a single individual in the cohort-arm of the UK10K study had a LoF allele (W297*) but did not have an extreme glycaemic phenotype. This individual’s fasting glucose and insulin concentrations were within the range of 95% of the values for this population. Nine high-confidence LoF variants in *GLP1R* were observed in the ExAC database (19). Eight were singletons and the most common had a frequency of less than 1/10,000, highlighting the difficulty in restricting analyses to individual LoF variants.

Association of *GLP1R* variant with quantitative traits and comparison with effects observed in clinical trials of GLP1R agonists

To further characterise the extent to which the *GLP1R* variant associations mirrored the effects of GLP1R-agonist therapy, we compared genetic associations to the metabolic effects observed in

previously reported clinical trials (Fig. 3, table S2). GLP1R agonist therapy can result in lower fasting and post-challenge glucose, weight loss, a reduction in systolic blood pressure, reduced total- and LDL-cholesterol and an increase in resting heart rate. The effects of GLP1R-agonists on glycaemic measures (fasting glucose and 2-h glucose) were stronger than those on non-glycaemic factors (Fig. 3), which have been detectable only in some meta-analyses of clinical trials (20–23).

Using fasting glucose as the benchmark, the per-allele association of the genetic variant with glucose (-0.15 SDs [-0.20,-0.11], from Fig. 2) was 3.3-fold weaker than the effect observed for GLP1R-agonist treatment (-0.49 [-0.60,-0.37], from Fig. 3). We therefore rescaled the genetic associations to account for this difference, by multiplying the magnitude of all observed genetic associations by 3.3 (Fig. 3), and demonstrated that there was little difference between the magnitude of association of the *GLP1R* variant and effects observed in clinical trials beyond that expected by chance ($\alpha=0.0025$). An exception to this observation was the impact of GLP1R agonist therapy on weight in non-diabetic individuals when compared to the observed association between the variant and BMI ($p=2.6\times10^{-4}$, Cochrane's Q test) (table S2). The genetic variant was not associated with BMI (Fig. 3), whereas the agonist therapy caused a reduction in body mass in non-diabetic individuals but not in individuals with T2D (fig. S1, table S2). However, five of the six trials in non-diabetic individuals were performed in obese participants (table S3), whose higher starting weight may have enabled a greater weight loss.

GLP1R agonists appeared to have a greater effect on 2-h glucose than the magnitude of association observed for the variant ($p=2.1\times10^{-12}$, Cochrane's Q test) (Fig. 3; fig. S2; table S2). The difference was most pronounced in comparison to trials in individuals with T2D, among whom we observed heterogeneity in the effect of GLP1R agonists on 2-h glucose, even within drug class ($I^2=97\%$) (fig. S2B). There was no significant difference between the magnitude of genetic association and the impact of GLP1R agonist therapy on 2-h glucose in non-diabetic individuals (Fig. 3; table S2), although the number of people included in such trials was much smaller than in trials including individuals with T2D (table S3).

Association of *GLP1R* variant with disease outcomes

Our final aim was to describe the association of the *GLP1R* variant with CHD and other outcomes. In a large-scale international collaboration, we studied 61,846 individuals with CHD and 163,728 controls, and found that the fasting glucose–lowering allele of *GLP1R* was associated with protection against CHD (Fig. 4). The association with CHD is greater than the 1% reduction in risk that would be predicted based on the association of this variant with fasting glucose alone (24) (see Supplementary Methods on “Calculating the reduction in coronary heart disease risk attributable to lower fasting glucose levels”), suggesting that lowering of fasting glucose alone is unlikely to explain the observed association between the *GLP1R* variant and lower risk of CHD. Although not significant, carriage of the minor allele was associated with lower LDL cholesterol, triglycerides, systolic blood pressure, and higher HDL cholesterol.

Using data from international consortia, we found no evidence for association of the *GLP1R* variant with pancreatic cancer, although the confidence intervals were wide owing to the comparatively small sample size (4987 cases and 8627 controls) and low frequency of the allele (Fig. 4). There was no evidence of association with breast, ovarian, or prostate cancer risk. Given the interest in GLP1R agonist therapy for neurological disease, including Parkinson’s (25) and Alzheimer’s (26), we also investigated the association of the *GLP1R* variant with those diseases, but found no evidence of association (Fig. 4).

Discussion

Anticipating the side effects of drugs prior to phase III clinical trials could support drug discovery and development, reducing attrition rates and saving considerable time and money. The promise of human genetics in this endeavour (2, 3, 7, 27) depends on the availability of genetic variants that mimic pharmaceutical interventions. We undertook a systematic study to identify such genetic

variants in the context of diabetes and obesity, and identified an association between fasting glucose and T2D with a missense variant in *GLP1R*, the gene encoding the GLP-1 receptor—the target of the GLP1R agonist class of T2D therapies. Regulatory authorities require evidence that therapies for T2D are not associated with unacceptable increases in cardiovascular risk. The reduced risk associated with the glucose-lowering genetic variant in *GLP1R* provides evidence that not only will GLP1R agonists meet this regulatory hurdle, but they may also reduce CHD events. Ongoing trials of GLP1R agonists are designed to resolve this uncertainty and will also augment the evidence on the broader validity of genetic approaches in drug-target validation.

A key consideration in assessing whether genetic variants can be used to understand therapeutic effects is how well the genetic variant mirrors the effects of pharmacological intervention at the same target. Genetic association data, here and reported previously (18), suggest that lifelong carriage of the minor *GLP1R* allele (at rs10305492) is associated with lower fasting glucose and lower risk of T2D, although not with 2-h glucose. Clinical trial data from individuals with T2D, who may have a diminished incretin effect, show that GLP1R agonists lower 2-h glucose considerably (28), whereas the effect on 2-h glucose is smaller in individuals without T2D (29), presumably because non-diabetic individuals are less likely to have an impaired incretin effect requiring therapeutic correction. Similarly, GLP1R agonists were associated with greater weight loss in obese individuals than in non-obese. Such a phenomenon has previously been suggested for the effects of GLP1R-agonism on blood pressure, where GLP1R-agonist therapy appears to lower blood pressure in individuals with high blood pressure but not in non-hypertensive individuals (30, 31). This highlights a limitation in the use of genetic variants in target validation: that the association of genetic variants is often tested in individuals of “normal” physiology, whereas clinical trials are generally performed in individuals with prevalent disease.

An important step in evaluating the utility of genomics in target validation is to understand the functional consequences of variants. For potential novel targets, whether the variant confers gain or loss of function informs the development of either an agonist or antagonist therapy. For

example, LoF variants have been used to understand the consequences of antagonism of a novel drug target (7, 32). However, researchers have gained insights using variants validated as instruments when their phenotypic associations mirrored pharmacological action, even in the absence of strong functional insights into the mechanism of those variants (33). GLP1R-agonist therapy reduces fasting glucose in humans, as does administration of GLP1, regardless of the duration or severity of T2D (34). In mice, the loss of GLP1R leads to fasting hyperglycaemia (35, 36). Together, these findings in humans and in mice suggest that the glucose-lowering minor allele at rs10305492 confers gain of function. However, differences in basal activity of the human and murine GLP1R (37) limit our ability to extrapolate findings from *GLP1R* knockout mice to humans (15, 32). Previous attempts to characterise the effect of this variant in cellular models have been inconclusive (38, 39). The rarity of putative LoF alleles in the *GLP1R* impaired our ability to restrict analyses to such variants. Although the absence of definitive functional characterisation is a limitation of this study, our observation that the minor allele is strongly associated with lower fasting glucose levels and is protective against T2D supports the validity of the variant as a genetic instrument for GLP1R-agonist therapy. Future integration of large-scale human genetic data with functional characterisation in appropriate cell models will allow broader application of variants, other than those characterised as LoF, in target validation.

Although the *GLP1R* variant was not associated with any of the other non-glycaemic or quantitative cardiovascular parameters, there was insufficient evidence to suggest the genetic associations and pharmacological effects were different. Power calculations indicated that, to detect the expected association with systolic blood pressure or resting heart rate, a sample size of more than 250,000 individuals would be required. This is considerably larger than most current genetic consortia, although this limitation could soon be overcome as larger studies become available (40), further strengthening the promise of genomics in target validation. Although we did not observe overall evidence for association of variants other than the *GLP1R* variant, the discovery phase, from which we selected variants for follow-up, was relatively small in comparison to the overall sample

and there remains a possibility of type II error in the discovery phase. As larger resources of genetic data become available, these potential concerns will also be reduced.

The detection of rare adverse effects of a drug remains a challenge. Pharmacoepidemiological approaches using routine database analysis may identify rare adverse outcomes associated with treatment, but the approach is rarely conclusive because of confounding, particularly by indication. Our demonstration that the *GLP1R* variant is not associated with pancreatic, breast, prostate, or ovarian cancer, or with Parkinson's or Alzheimer's disease is limited by the upper bounds of the confidence intervals, which are too high to allow strong inference about the likely long-term safety of GLP1R agonists with regard to these outcomes. Although these data represent the largest resources available globally, the accumulation of studies with greater numbers of individuals with genetic data and robust disease outcome classification will considerably enhance the potential of this type of investigation. The comparisons of other traits and disease outcomes, beyond the primary indications, makes the assumption that pharmacological effects are mediated via "on-target" effects and not "off-target" effects (i.e. those mediated by effects of the agent on other non-specific targets). Although our results offer insight into the effects of GLP1R agonists, they do not necessarily apply to other agents targeting the incretin pathway through different mechanisms, such as by DPP-4 inhibition (41).

In conclusion, through a targeted exome sequencing approach, we identified that a low-frequency missense variant in *GLP1R* was associated with lower fasting glucose and risk of T2D, similar to the effects of GLP1R agonist therapy. This variant was also associated with lower risk of CHD, thus providing supportive evidence that these agents are not likely to be associated with an unacceptable increase in cardiovascular risk and may indeed be associated with benefit, a question currently being addressed in randomised controlled trials. We propose that future drug development and investment decisions could be informed by genomic data much earlier in the development process, providing insight into both efficacy and side-effects.

Methods

Study design

We studied six genes encoding therapeutic targets licensed or in development for obesity or T2D (*CNR2*, *DPP4*, *GLP1R*, *SLC5A1*, *HTR2C*, *MCHR1*), drawn from a recent targeted exome sequencing study of 202 genes encoding drug targets (8), which represented approximately 1% of the coding genome and 7% of all genes considered current or potential drug targets (8). In the “Discovery Analysis”, we investigated the association of common and rare variants in these six genes with seven T2D and obesity-related traits (Fig. 1). We analysed all variants which had i) $MAF \geq 0.5\%$ or well imputed ($R^2 > 0.5$) in CoLaus; ii) $MAF \geq 0.5\%$ in GEMS; or iii) $MAF \geq 0.1\%$ in BMI (given the larger sample size) in the CoLaus study (42), the GEMS study (43), or all individuals with BMI measurements. We examined 121 variants for association with six traits in the CoLaus study ($6 \times 121 = 726$ tests); 4 traits in GEMS ($4 \times 121 = 484$ tests); and 1 trait in the BMI study, comprising a total of 1331 tests of association. First, we analysed a subset of the population-based CoLaus study ($n=2086$) for T2D, obesity, waist circumference, fasting glucose, fasting insulin, and 2-h glucose traits. Second, in the GEMS dyslipidaemic case and normolipidaemic control study ($n_{\text{cases}}=787$, $n_{\text{controls}}=792$), we analysed obesity, waist circumference, fasting glucose, and fasting insulin traits. We performed discovery analyses in the CoLaus and GEMS studies separately due to the different study designs and traits analysed in attempt to maximise sensitivity to detect associations that might be masked by context-dependent associations. Third, BMI measures were available in a larger sample size from 11 studies (Fig. 1), and were analysed together. We provide the sample sizes for the discovery analyses in Figure 1 and trait-specific sample sizes in Table 1 ($n = 505 - 11,806$). We augmented the sequence data for the CoLaus study with imputed data in the remainder of the study ($n=3539$) where variants were imputable ($R^2 > 0.5$) using a custom imputation process on individuals genotyped on the Affymetrix 500K chip but not included in the targeted sequencing experiment (Supplementary Materials).

Using results from the discovery analyses, we identified variants that were associated with T2D or obesity-related traits at the $p < 0.001$ level or were located in genes encoding targets of strategic interest to GSK, including *GLP1R*, *DPP4*, *CNR2*, and *HTR2C* with a p value threshold of < 0.05 . To maximise sensitivity to detect associations in these genes of highest interest, we took forward to follow up those variants reaching $p < 0.05$ in the discovery analyses. However, this did not affect the threshold for statistical significance or overall alpha value (3.8×10^{-5}), for which we accounted for all association tests performed in the discovery analyses ($N = 1331$). The principal reason for prioritising specific genes was to ensure a balance between sensitivity for targets of high priority to GSK and to maintain specificity: given that initial replication was performed by de novo large-scale targeted genotyping, we were practically unable to follow up vast numbers of variants. This does not bias the variants selected for follow-up, nor raise the risk of type I error. Indeed, the only variant we determined to be mimicking pharmacological manipulation was well beyond “genome-wide significance” even if all possible low-frequency and common variants in the genome had been tested.

We then genotyped seven variants in six genes in up to 39,979 follow-up participants of European ancestry drawn from multiple studies (Fig. 1): CoLaus (when GEMS was the discovery sample), GEMS (when CoLaus was the discovery set), Ely (44) ($n = 1722$), EPIC-Norfolk (45) ($n = 25313$), Fenland (46) ($n = 6379$), and LOLIPOP (47) ($n = 6565$) studies. The follow-up analysis of T2D included participants from the Norfolk Diabetes Study ($N_{\text{cases}} = 5587$ and $N_{\text{controls}} = 19012$), GenOA study ($N_{\text{cases}} = 129$ and $N_{\text{controls}} = 1501$), and individuals with T2D from the ADDITION study (48) ($N_{\text{cases}} = 816$) who were combined with additional cases from the Ely study ($N_{\text{cases}} = 116$) and compared to non-diabetic controls from the Ely study ($N_{\text{controls}} = 1487$).

We also sought further *in silico* follow-up Analysis to further evaluate associations in collaborative studies utilizing results from the MAGIC and CHARGE consortia. Five of the seven variants were available for in silico analysis (table 1). Further details on each of the studies and consortia are provided in the Supplementary Materials and table S1 and S4.

Statistical analyses

We carried out genetic association analyses on variants identified via targeted sequencing using an additive genetic model by linear or logistic regression, adjusting for age and sex and other study-specific covariates. We combined study-specific estimates using fixed effect meta-analysis. We performed analyses on standardised variables (mean=0 and SD =1) and, as such, expressed effect sizes as standard deviations (SDs) for quantitative traits. In total, we analysed 121 single nucleotide variants (SNVs). Overall, we performed 1,331 tests of association in the discovery analyses and, as such, associations that were $\alpha < 3.8 \times 10^{-5}$ in the combined analysis were deemed to be statistically significant.

We performed targeted genotyping of selected variants from discovery analyses using Sequenom for the Ely, EPIC-Norfolk, Fenland, and ADDITION studies and KASPar for the LOLIPOP study. Imputed data were also available in the GenOA study using reference haplotypes from participants in the previous sequencing study (8). We carried out genetic association analyses in each study under an additive genetic model using linear or logistic regression, again adjusting for age, sex and study-specific covariates. We sought further *in silico* follow-up from summary association results from MAGIC and CHARGE consortia (table 1). We converted summary association result effect sizes to SDs using the SD of fasting glucose from the population-based Fenland study (SD = 0.65 mM) (46). We meta-analyzed results from the discovery analysis, follow-up analysis and *in silico* follow-up analysis using a fixed effect, inverse-variance weighted approach. The discovery analysis of the CoLaus study included association results from the sequence variants and imputed variants (table 1). In the entire CoLaus study, we later directly genotyped (KASPar technology) variants which had been imputed in the unsequenced CoLaus participants study as part of the original follow-up analysis. The combined analysis results in table 1 therefore represent those from the directly genotyped data.

For variants that showed statistically significant associations in the combined analysis ($p < 3.8 \times 10^{-5}$), we investigated their association with a range of anthropometric, metabolic, and cardiovascular risk factors and disease outcomes in the studies described previously, as well as in additional studies described in table S1 and S4 and in Supplementary Materials. We also investigated the association of variants reaching statistical significance after follow up ($\alpha < 3.8 \times 10^{-5}$) with coronary heart disease (CHD) through targeted genotyping and collaboration with large-scale Exome chip consortia (table S1). For these variants, we also investigated association with a range of other disease outcomes (table S1), with a particular focus on diseases previously suggested as potential opportunities for repositioning (i.e. where existing drugs might be used for alternative indications). However, as the variant reaching statistical significance was not well covered on existing GWAS arrays or in HapMap, we were limited to those disease outcomes for which we could obtain association data. For genes that contained variants with $p < 3.8 \times 10^{-5}$ in the combined analysis, we investigated the presence of putative LoF alleles in individuals in whom we had performed targeted sequencing (8) and in individuals with whole-genome sequencing from the UK10K study (www.uk10k.org).

Comparison of clinical trial effects and genetic associations

Randomized clinical trials of GLP1R-agonists were identified through previous systematic reviews and by performing a supplementary literature search, as detailed in the Supplementary Materials. Only trials with placebo or no-drug comparison groups (i.e. no trials with active comparison groups), with ≥ 4 weeks drug treatment (i.e. no single dose studies) and ≥ 10 participants per trial arm were included. Treatment effects were expressed in SDs before pooling across trials using random effects meta-analysis (see table S3 for details of clinical trials included). P-values derived from Cochrane's Q test were used as a guide to assess whether there were pairwise differences between the rescaled genetic and trial estimates.

Table 1. Discovery, follow-up, and combined results for variants taken forward to follow-up. Seven variants in six genes reached $p < 0.001$ (or $p < 0.05$ in target of interest to GSK) in sequence-based discovery analyses (Fig. 1) and were taken forward to follow-up in additional samples, by targeted genotyping and by *in silico* lookup from existing consortia. Data and P values are from fixed effect meta-analysis of linear regression for quantitative traits or logistic regression for binary disease status.

Gene	Variant	Chr	Position (NCBI b37 genome alignment)	Consequence	Trait	Effect allele	Other allele	MAF	Stage	Study	n (case/control for binary trait)	Beta (Odds ratio for binary trait)	se [CI for OR]	P -value
GLP1R	rs10305492	6	39046794	A316T	Fasting glucose	A	G	0.015	Discovery	Sequenced CoLaus*	1869	-0.28	0.14	0.04
									Targeted follow-up	Additional CoLaus, ELY, Fenland, LOLIPOP, GEMS	18,937	-0.13	0.04	1.5×10^{-3}
									In silico follow-up	MAGIC (29)	20,077	-0.16	0.03	1.1×10^{-7}
									Combined		40,883	-0.15	0.02	2.6×10^{-10}
DPP4	rs56179129	2	162890142	V266I	Fasting glucose	T	C	0.008	Discovery	GEMS	1416	0.61	0.21	3.6×10^{-3}
									Targeted follow-up	CoLaus, ELY, LOLIPOP	12934	0.00	0.07	0.95
									In silico follow-up	CHARGE Exome chip (18)	49838	0.00	0.03	0.16
									Combined		64188	0.01	0.03	0.71
SLC5A1	rs200410750	22	32439209	5' UTR	Fasting Glucose	T	C	0.001	Discovery	Sequenced and imputed CoLaus	5210	1.44	0.33	1.7×10^{-5}
									Targeted follow-up	ELY, Fenland, LOLIPOP	12707	-0.16	0.27	0.56
									In silico follow-up	n/a				NA
									Combined		18059	0.51	0.19	0.01
CNR2	rs4649124	1	24201357	Synonymous	2 hour glucose	A	G	0.420	Discovery	Sequenced and imputed CoLaus	505	0.18	0.06	0.01
									Targeted follow-up	ELY, Fenland	6377	0.00	0.02	0.95
									In silico follow-up	MAGIC (proxy: rs10917431)(49)	15234	-0.01	0.01	0.49
									Combined		22106	0.00	0.01	0.88
CNR2	rs2229579	1	24201162	H316Y	T2D	T	C	0.110	Discovery	Sequenced and imputed CoLaus	385/5241	0.73	[0.55, 0.97]	0.03
									Targeted follow-up	ADDITION-ELY, NDS, LOLIPOP, GenOA	7141/27096	1.06	[0.99, 1.14]	0.07
									In silico follow-up	CHARGE Exome chip (18)	9524/60718	0.96	[0.90, 1.01]	0.10
									Combined		17047/93225	0.99	[0.95, 1.04]	0.67

<i>HTR2C</i>	rs56372597	X	113951968	Intronic	BMI	A	G	0.150	Discovery	BMI	10798	0.05	0.02	2.1x10 ⁻³
									Targeted follow-up	Additional CoLaus, ELY, EPIC, Fenland, LOLIPOP	36983	0.00	0.01	0.92
									In silico	n/a				NA
									follow-up					
									Combined		47781	0.01	0.01	0.13
<i>MCHR1</i>	rs117372135	22	41075523	T25M	BMI	T	C	0.002	Discovery	BMI	10952	0.62	0.15	4.5x10 ⁻⁵
									Targeted follow-up	Additional CoLaus, ELY, EPIC, Fenland, LOLIPOP	37240	0.08	0.10	0.40
									In silico	CHARGE adiposity Exome chip	68978	-0.04	0.07	0.59
									follow-up	working group				
									Combined		117170	0.08	0.05	0.13

*Analyzed in sequenced CoLaus participants only owing to low imputation quality ($R^2 < 0.5$) in additional CoLaus participants at the discovery stage. #Not analyzed in GEMS due to low number of carriers (< 5 minor alleles)

Figure legends

Figure 1. Overall study design, participating studies, and consortia. Discovery analyses were performed using targeted exome sequencing of variation in six genes tested for association with seven traits. Variants were taken forward to follow-up by targeted genotyping. Additional *in silico* results were obtained using available association results. Combined results were obtained by fixed-effect meta-analysis of estimates from linear or logistic regression, as appropriate. Based on the 1331 statistical tests performed in discovery analyses, $p < 3.8 \times 10^{-5}$ was used as the threshold for statistical significance. In targeted genotyping, (g) refers to studies that were directly genotyped for relevant markers, whereas (i) indicates those in which relevant variants were captured by imputation.

Figure 2. Association of *GLP1R* variant (rs10305492) with glycaemic traits. (A) Genetic variant association with glycaemic traits. Data are standard deviations per minor allele at rs10305492. Fasting glucose results are from the combined analysis (Table 1). Individual studies contributing to the associations for fasting insulin and 2-h glucose are in table S4. All results reflect point estimates and 95% confidence intervals (CI) from a fixed-effect meta-analysis of linear regression estimates. (B) Effect size of the *GLP1R* variant (in red) and loci previously reported to be associated with fasting glucose. Effect sizes are reported from discovery analyses of available MAGIC results (50), and from the combined estimate for the *GLP1R* variant in (A).

Figure 3. Comparison of *GLP1R* variant (rs10305492) associations with effects observed in clinical trials of *GLP1R* agonists in non-diabetic individuals and in individuals with T2D. Genetic associations are all scaled to match the effects of *GLP1R*-agonists on fasting glucose (i.e. per 3.3 copies of the minor (A) allele). Genetic variant results are beta estimates and 95% confidence intervals from fixed effect meta-analysis of linear regression results. Trial results are estimates from fixed-effect meta-analyses of standardised mean differences between treatment and comparison groups of the individual trials listed in table S3. *Trials reported effects on body mass, whereas genetic associations were only available for BMI.

Figure 4. Association of *GLP1R* variant (rs10305492) with disease outcomes. Association with disease outcomes are reported per-minor allele at rs10305492. Data show odds ratios and 95% confidence intervals from logistic regression models.

Supplementary materials

Figure S1. Effects of *GLP1R* agonists on body weight.

Figure S2. Effects of *GLP1R*-agonists on 2h glucose.

Table S1. Study characteristics for disease traits.

Table S2. Comparison of heterogeneity between trial and rescaled genetic estimates.

Table S3. Details of randomized trials contributing to analyses of *GLP1R*-agonist effects included in Fig. 2

Table S4. Study characteristics for quantitative traits.

References and notes

1. US FDA, Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes (2008). (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf>)
2. R. M. Plenge, E. M. Scolnick, D. Altshuler, Validating therapeutic targets through human genetics., *Nat. Rev. Drug Discov.* **12**, 581–594 (2013).
3. M. R. Nelson, H. Tipney, J. L. Painter, J. Shen, P. Nicoletti, Y. Shen, A. Floratos, P. C. Sham, M. J. Li, J. Wang, L. R. Cardon, J. C. Whittaker, P. Sanseau, The support of human genetic evidence for approved drug indications, *Nat. Genet.* **47**, 856–860 (2015).
4. B. F. Voight, G. M. Peloso, M. Orho-Melander, R. Frikke-Schmidt, M. Barbalic, M. K. Jensen, G. Hindy, H. Hólm, E. L. Ding, T. Johnson, H. Schunkert, N. J. Samani, R. Clarke, J. C. Hopewell, J. F. Thompson, M. Li, G. Thorleifsson, C. Newton-Cheh, K. Musunuru, J. P. Pirruccello, D. Saleheen, L. Chen, A. F. R. Stewart, A. Schillert, U. Thorsteinsdottir, G. Thorgeirsson, S. Anand, J. C. Engert, T. Morgan, J. Spertus, M. Stoll, K. Berger, N. Martinelli, D. Girelli, P. P. McKeown, C. C. Patterson, S. E. Epstein, J. Devaney, M.-S. Burnett, V. Mooser, S. Ripatti, I. Surakka, M. S. Nieminen, J. Sinisalo, M.-L. Lokki, M. Perola, A. Havulinna, U. de Faire, B. Gigante, E. Ingelsson, T. Zeller, P. Wild, P. I. W. de Bakker, O. H. Klungel, A.-H. Maitland-van der Zee, B. J. M. Peters, A. de Boer, D. E. Grobbee, P. W. Kamphuisen, V. H. M. Deneer, C. C. Elbers, N. C. Onland-Moret, M. H. Hofker, C. Wijmenga, W. M. M. Verschuren, J. M. a Boer, Y. T. van der Schouw, A. Rasheed, P. Frossard, S. Demissie, C. Willer, R. Do, J. M. Ordovas, G. R. Abecasis, M. Boehnke, K. L. Mohlke, M. J. Daly, C. Guiducci, N. P. Burt, A. Sur, E. Gonzalez, S. Purcell, S. Gabriel, J. Marrugat, J. Peden, J. Erdmann, P. Diemert, C. Willenborg, I. R. König, M. Fischer, C. Hengstenberg, A. Ziegler, I. Buyschaert, D. Lambrechts, F. Van de Werf, K. a Fox, N. E. El Mokhtari, D. Rubin, J. Schrezenmeir, S. Schreiber, A. Schäfer, J. Danesh, S. Blankenberg, R. Roberts, R. McPherson, H. Watkins, A. S. Hall, K. Overvad, E. Rimm, E. Boerwinkle, A. Tybjaerg-Hansen, L. A. Cupples, M. P. Reilly, O. Melander, P. M. Mannucci, D. Ardisino, D. Siscovick, R. Elosua, K. Stefansson, C. J. O'Donnell, V. Salomaa, D. J. Rader, L. Peltonen, S. M. Schwartz, D. Altshuler, S. Kathiresan, Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study., *Lancet* **380**, 572–80 (2012).
5. J. Zacho, A. Tybjaerg-Hansen, J. S. Jensen, P. Grande, H. Sillesen, B. G. Nordestgaard, Genetically elevated C-reactive protein and ischemic vascular disease., *N. Engl. J. Med.* **359**, 1897–1908 (2008).
6. J. C. Cohen, E. Boerwinkle, T. H. Mosley, H. H. Hobbs, Sequence variations in PCSK9, low LDL, and protection against coronary heart disease., *N. Engl. J. Med.* **354**, 1264–72 (2006).
7. Myocardial Infarction Genetics Consortium Investigators, Inactivating Mutations in NPC1L1 and Protection from Coronary Heart Disease, *N. Engl. J. Med.* , 141112140016008 (2014).
8. M. R. Nelson, D. Wegmann, M. G. Ehm, D. Kessner, P. St Jean, C. Verzilli, J. Shen, Z. Tang, S.-A. Bacanu, D. Fraser, L. Warren, J. Aponte, M. Zawistowski, X. Liu, H. Zhang, Y. Zhang, J. Li, Y. Li, L. Li, P. Woollard, S. Topp, M. D. Hall, K. Nangle, J. Wang, G. Abecasis, L. R. Cardon, S. Zöllner, J. C. Whittaker, S. L. Chisoe, J. Novembre, V. Mooser, An abundance of rare functional variants in 202 drug target genes sequenced in 14,002 people., *Science* **337**, 100–4 (2012).
9. A. Keinan, A. G. Clark, Recent explosive human population growth has resulted in an excess of rare genetic variants., *Science* **336**, 740–3 (2012).

10. J. A. Tennessen, A. W. Bigam, T. D. O'Connor, W. Fu, E. E. Kenny, S. Gravel, S. McGee, R. Do, X. Liu, G. Jun, H. M. Kang, D. Jordan, S. M. Leal, S. Gabriel, M. J. Rieder, G. Abecasis, D. Altshuler, D. a Nickerson, E. Boerwinkle, S. Sunyaev, C. D. Bustamante, M. J. Bamshad, J. M. Akey, Evolution and functional impact of rare coding variation from deep sequencing of human exomes., *Science* **337**, 64–9 (2012).
11. A. Coventry, L. M. Bull-Otterson, X. Liu, A. G. Clark, T. J. Maxwell, J. Crosby, J. E. Hixson, T. J. Rea, D. M. Muzny, L. R. Lewis, D. a Wheeler, A. Sabo, C. Lusk, K. G. Weiss, H. Akbar, A. Cree, A. C. Hawes, I. Newsham, R. T. Varghese, D. Villasana, S. Gross, V. Joshi, J. Santibanez, M. Morgan, K. Chang, W. H. Iv, A. R. Templeton, E. Boerwinkle, R. Gibbs, C. F. Sing, Deep resequencing reveals excess rare recent variants consistent with explosive population growth., *Nat. Commun.* **1**, 131 (2010).
12. W. Fu, T. D. O'Connor, G. Jun, H. M. Kang, G. Abecasis, S. M. Leal, S. Gabriel, M. J. Rieder, D. Altshuler, J. Shendure, D. a Nickerson, M. J. Bamshad, J. M. Akey, Analysis of 6,515 exomes reveals the recent origin of most human protein-coding variants., *Nature* **493**, 216–20 (2013).
13. J. A. Lovshin, D. J. Drucker, Incretin-based therapies for type 2 diabetes mellitus., *Nat. Rev. Endocrinol.* **5**, 262–9 (2009).
14. P. Cure, A. Pileggi, R. Alejandro, Exenatide and rare adverse events., *N. Engl. J. Med.* **358**, 1969–70; discussion 1971–2 (2008).
15. A. Astrup, S. Rössner, L. Van Gaal, A. Rissanen, L. Niskanen, M. Al Hakim, J. Madsen, M. F. Rasmussen, M. E. J. Lean, NN8022-1807 Study Group, Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study., *Lancet (London, England)* **374**, 1606–16 (2009).
16. M. A. Pfeffer, B. Claggett, R. Diaz, K. Dickstein, H. C. Gerstein, L. V. Køber, F. C. Lawson, L. Ping, X. Wei, E. F. Lewis, A. P. Maggioni, J. J. V. McMurray, J. L. Probstfield, M. C. Riddle, S. D. Solomon, J.-C. Tardif, Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome, *N. Engl. J. Med.* **373**, 2247–2257 (2015).
17. J. Sivertsen, J. Rosenmeier, J. J. Holst, T. Vilsbøll, The effect of glucagon-like peptide 1 on cardiovascular risk., *Nat. Rev. Cardiol.* **9**, 209–22 (2012).
18. J. Wessel, A. Y. Chu, S. M. Willems, S. Wang, H. Yaghootkar, J. A. Brody, M. Dauriz, M.-F. Hivert, S. Raghavan, L. Lipovich, B. Hidalgo, K. Fox, J. E. Huffman, P. An, Y. Lu, L. J. Rasmussen-Torvik, N. Grarup, M. G. Ehm, L. Li, A. S. Baldridge, A. Stančáková, R. Abrol, C. Besse, A. Boland, J. Bork-Jensen, M. Fornage, D. F. Freitag, M. E. Garcia, X. Guo, K. Hara, A. Isaacs, J. Jakobsdottir, L. A. Lange, J. C. Layton, M. Li, J. Hua Zhao, K. Meidtner, A. C. Morrison, M. A. Nalls, M. J. Peters, M. Sabater-Lleal, C. Schurmann, A. Silveira, A. V Smith, L. Southam, M. H. Stoiber, R. J. Strawbridge, K. D. Taylor, T. V Varga, K. H. Allin, N. Amin, J. L. Aponte, T. Aung, C. Barbieri, N. A. Bihlmeyer, M. Boehnke, C. Bombieri, D. W. Bowden, S. M. Burns, Y. Chen, Y.-D. Chen, C.-Y. Cheng, A. Correa, J. Czajkowski, A. Dehghan, G. B. Ehret, G. Eiriksdottir, S. A. Escher, A.-E. Farmaki, M. Frånberg, G. Gambaro, F. Giulianini, W. A. Goddard, A. Goel, O. Gottesman, M. L. Grove, S. Gustafsson, Y. Hai, G. Hallmans, J. Heo, P. Hoffmann, M. K. Ikram, R. A. Jensen, M. E. Jørgensen, T. Jørgensen, M. Karaleftheri, C. C. Khor, A. Kirkpatrick, A. T. Kraja, J. Kuusisto, E. M. Lange, I. T. Lee, W.-J. Lee, A. Leong, J. Liao, C. Liu, Y. Liu, C. M. Lindgren, A. Linneberg, G. Malerba, V. Mamakou, E. Marouli, N. M. Maruthur, A. Matchan, R. McKean-Cowdin, O. McLeod, G. A. Metcalf, K. L. Mohlke, D. M. Muzny, I. Ntalla, N. D. Palmer, D. Pasko, A. Peter, N. W. Rayner, F. Renström, K. Rice, C. F. Sala, B. Sennblad, I. Serafetinidis, J. A. Smith, N. Soranzo, E. K. Speliotes, E. A. Stahl, K. Stirrups, N. Tentolouris, A. Thanopoulou, M. Torres, M. Traglia, E. Tsafantakis, S. Javad, L. R. Yanek, E. Zengini, D. M. Becker, J. C. Bis, J. B. Brown, L. Adrienne Cupples, T. Hansen, E. Ingelsson, A. J. Karter, C. Lorenzo, R. A. Mathias, J. M. Norris, G. M. Peloso, W. H.-H. Sheu, D. Toniolo, D. Vaidya, R. Varma, L. E. Wagenknecht, H. Boeing, E. P. Bottinger, G.

Dedoussis, P. Deloukas, E. Ferrannini, O. H. Franco, P. W. Franks, R. A. Gibbs, V. Gudnason, A. Hamsten, T. B. Harris, A. T. Hattersley, C. Hayward, A. Hofman, J.-H. Jansson, C. Langenberg, L. J. Launer, D. Levy, B. A. Oostra, C. J. O'Donnell, S. O'Rahilly, S. Padmanabhan, J. S. Pankow, O. Polasek, M. A. Province, S. S. Rich, P. M. Ridker, I. Rudan, M. B. Schulze, B. H. Smith, A. G. Uitterlinden, M. Walker, H. Watkins, T. Y. Wong, E. Zeggini, M. Laakso, I. B. Borecki, D. I. Chasman, O. Pedersen, B. M. Psaty, E. Shyong Tai, C. M. van Duijn, N. J. Wareham, D. M. Waterworth, E. Boerwinkle, W. H. Linda Kao, J. C. Florez, R. J. F. Loos, J. G. Wilson, T. M. Frayling, D. S. Siscovick, J. Dupuis, J. I. Rotter, J. B. Meigs, R. A. Scott, M. O. Goodarzi, Low-frequency and rare exome chip variants associate with fasting glucose and type 2 diabetes susceptibility., *Nat. Commun.* **6**, 5897 (2015).

19. Exome Aggregation Consortium, M. Lek, K. Karczewski, E. Minikel, K. Samocha, E. Banks, T. Fennell, A. O'Donnell-Luria, J. Ware, A. Hill, B. Cummings, T. Tukiainen, D. Birnbaum, J. Kosmicki, L. Duncan, K. Estrada, F. Zhao, J. Zou, E. Pierce-Hoffman, D. Cooper, M. DePristo, R. Do, J. Flannick, M. Fromer, L. Gauthier, J. Goldstein, N. Gupta, D. Howrigan, A. Kiezun, M. Kurki, A. L. Moonshine, P. Natarajan, L. Orozco, G. Peloso, R. Poplin, M. Rivas, V. Ruano-Rubio, D. Ruderfer, K. Shakir, P. Stenson, C. Stevens, B. Thomas, G. Tiao, M. Tusie-Luna, B. Weisburd, H.-H. Won, D. Yu, D. Altshuler, D. Ardissino, M. Boehnke, J. Danesh, E. Roberto, J. Florez, S. Gabriel, G. Getz, C. Hultman, S. Kathiresan, M. Laakso, S. McCarroll, M. McCarthy, D. McGovern, R. McPherson, B. Neale, A. Palotie, S. Purcell, D. Saleheen, J. Scharf, P. Sklar, S. Patrick, J. Tuomilehto, H. Watkins, J. Wilson, M. Daly, D. MacArthur. 2015. Analysis of protein-coding genetic variation in 60,706 humans. doi: 10.1101/030338

20. J. L. Moreno, K. C. Willett, A. R. Desilets, Exenatide as a novel weight loss modality in patients without diabetes., *Ann. Pharmacother.* **46**, 1700–6 (2012).

21. T. Vilsbøll, M. Christensen, A. E. Junker, F. K. Knop, L. L. Gluud, Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials., *BMJ* **344**, d7771 (2012).

22. L. E. Robinson, T. A. Holt, K. Rees, H. S. Randeva, J. P. O'Hare, Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: systematic review and meta-analysis., *BMJ Open* **3** (2013), doi:10.1136/bmjopen-2012-001986.

23. L. J. Schmidt, W. Habacher, T. Augustin, E. Krahulec, T. Semlitsch, A systematic review and meta-analysis of the efficacy of lixisenatide in the treatment of patients with type 2 diabetes., *Diabetes. Obes. Metab.* (2014), doi:10.1111/dom.12269.

24. The Emerging Risk Factors Collaboration, Diabetes mellitus, fasting glucose, and risk of cause-specific death., *N. Engl. J. Med.* **364**, 829–41 (2011).

25. A. Harkavyi, A. Abuirmeileh, R. Lever, A. E. Kingsbury, C. S. Biggs, P. S. Whitton, Glucagon-like peptide 1 receptor stimulation reverses key deficits in distinct rodent models of Parkinson's disease., *J. Neuroinflammation* **5**, 19 (2008).

26. Y. Li, K. B. Duffy, M. A. Ottinger, B. Ray, J. a Bailey, H. W. Holloway, D. Tweedie, T. Perry, M. P. Mattson, D. Kapogiannis, K. Sambamurti, D. K. Lahiri, N. H. Greig, GLP-1 receptor stimulation reduces amyloid-beta peptide accumulation and cytotoxicity in cellular and animal models of Alzheimer's disease., *J. Alzheimers. Dis.* **19**, 1205–19 (2010).

27. A. P. Gregory, C. a Dendrou, K. E. Attfield, A. Haghikia, D. K. Xifara, F. Butter, G. Poschmann, G. Kaur, L. Lambert, O. a Leach, S. Prömel, D. Punwani, J. H. Felce, S. J. Davis, R. Gold, F. C. Nielsen, R. M. Siegel, M. Mann, J. I. Bell, G. McVean, L. Fugger, TNF receptor 1 genetic risk mirrors outcome of anti-TNF therapy in multiple sclerosis., *Nature* **488**, 508–11 (2012).

28. L. L. Kjems, J. J. Holst, A. Vølund, S. Madsbad, The influence of GLP-1 on glucose-stimulated insulin secretion: effects on beta-cell sensitivity in type 2 and nondiabetic subjects., *Diabetes* **52**, 380–386 (2003).
29. J. Dushay, C. Gao, G. S. Gopalakrishnan, M. Crawley, E. K. Mitten, E. Wilker, J. Mullington, E. Maratos-Flier, Short-term exenatide treatment leads to significant weight loss in a subset of obese women without diabetes., *Diabetes Care* **35**, 4–11 (2012).
30. J. R. Ussher, D. J. Drucker, Cardiovascular actions of incretin-based therapies., *Circ. Res.* **114**, 1788–803 (2014).
31. M. Grimm, J. Han, C. Weaver, P. Griffin, C. T. Schulteis, H. Dong, J. Malloy, Efficacy, safety, and tolerability of exenatide once weekly in patients with type 2 diabetes mellitus: an integrated analysis of the DURATION trials., *Postgrad. Med.* **125**, 47–57 (2013).
32. J. Flannick, G. Thorleifsson, N. L. Beer, S. B. R. Jacobs, N. Grarup, N. P. Burt, A. Mahajan, C. Fuchsberger, G. Atzmon, R. Benediktsson, J. Blangero, D. W. Bowden, I. Brandslund, J. Brosnan, F. Burslem, J. Chambers, Y. S. Cho, C. Christensen, D. A. Douglas, R. Duggirala, Z. Dymek, Y. Farjoun, T. Fennell, P. Fontanillas, T. Forsén, S. Gabriel, B. Glaser, D. F. Gudbjartsson, C. Hanis, T. Hansen, A. B. Hreidarsson, K. Hveem, E. Ingelsson, B. Isomaa, S. Johansson, T. Jørgensen, M. E. Jørgensen, S. Kathiresan, A. Kong, J. Kooner, J. Kravic, M. Laakso, J.-Y. Lee, L. Lind, C. M. Lindgren, A. Linneberg, G. Masson, T. Meitinger, K. L. Mohlke, A. Molven, A. P. Morris, S. Potluri, R. Rauramaa, R. Ribel-Madsen, A. Richard, T. Rolph, V. Salomaa, A. V. Segrè, H. Skärstrand, V. Steinthorsdottir, H. M. Stringham, P. Sulem, E. S. Tai, Y. Y. Teo, T. Teslovich, U. Thorsteinsdottir, J. K. Trimmer, T. Tuomi, J. Tuomilehto, F. Vaziri-Sani, B. F. Voight, J. G. Wilson, M. Boehnke, M. I. McCarthy, P. R. Njølstad, O. Pedersen, L. Groop, D. R. Cox, K. Stefansson, D. Altshuler, Loss-of-function mutations in SLC30A8 protect against type 2 diabetes., *Nat. Genet.* **46**, 357–63 (2014).
33. D. I. Swerdlow, D. Preiss, K. B. Kuchenbaecker, M. V Holmes, J. E. L. Engmann, T. Shah, R. Sofat, S. Stender, P. C. D. Johnson, R. a Scott, M. Leusink, N. Verweij, S. J. Sharp, Y. Guo, C. Giambartolomei, C. Chung, A. Peasey, A. Amuzu, K. Li, J. Palmen, P. Howard, J. a Cooper, F. Drenos, Y. R. Li, G. Lowe, J. Gallacher, M. C. W. Stewart, I. Tzoulaki, S. G. Buxbaum, D. L. van der A, N. G. Forouhi, N. C. Onland-Moret, Y. T. van der Schouw, R. B. Schnabel, J. a Hubacek, R. Kubinova, M. Baceviciene, A. Tamosiunas, A. Pajak, R. Topor-Madry, U. Stepaniak, S. Malyutina, D. Baldassarre, B. Sennblad, E. Tremoli, U. de Faire, F. Veglia, I. Ford, J. W. Jukema, R. G. J. Westendorp, G. J. de Borst, P. a de Jong, A. Algra, W. Spiering, A. H. M. der Zee, O. H. Klungel, A. de Boer, P. a Doevendans, C. B. Eaton, J. G. Robinson, D. Duggan, J. Kjekshus, J. R. Downs, A. M. Gotto, A. C. Keech, R. Marchioli, G. Tognoni, P. S. Sever, N. R. Poulter, D. D. Waters, T. R. Pedersen, P. Amarenco, H. Nakamura, J. J. V McMurray, J. D. Lewsey, D. I. Chasman, P. M. Ridker, A. P. Maggioni, L. Tavazzi, K. K. Ray, S. R. K. Seshasai, J. E. Manson, J. F. Price, P. H. Whincup, R. W. Morris, D. a Lawlor, G. D. Smith, Y. Ben-Shlomo, P. J. Schreiner, M. Fornage, D. S. Siscovick, M. Cushman, M. Kumari, N. J. Wareham, W. M. M. Verschuren, S. Redline, S. R. Patel, J. C. Whittaker, A. Hamsten, J. a Delaney, C. Dale, T. R. Gaunt, A. Wong, D. Kuh, R. Hardy, S. Kathiresan, B. a Castillo, P. van der Harst, E. J. Brunner, A. Tybjaerg-Hansen, M. G. Marmot, R. M. Krauss, M. Tsai, J. Coresh, R. C. Hoogeveen, B. M. Psaty, L. a Lange, H. Hakonarson, F. Dudbridge, S. E. Humphries, P. J. Talmud, M. Kivimäki, N. J. Timpson, C. Langenberg, F. W. Asselbergs, M. Voevod, M. Bobak, H. Pikhart, J. G. Wilson, A. P. Reiner, B. J. Keating, A. D. Hingorani, N. Sattar, HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials, *Lancet* , 1–11 (2014).
34. M. B. Toft-Nielsen, S. Madsbad, J. J. Holst, Determinants of the effectiveness of glucagon-like peptide-1 in type 2 diabetes, *J. Clin. Endocrinol. Metab.* **86**, 3853–3860 (2001).
35. L. A. Scrocchi, T. J. Brown, N. MaClusky, P. L. Brubaker, A. B. Auerbach, A. L. Joyner, D. J. Drucker,

Glucose intolerance but normal satiety in mice with a null mutation in the glucagon-like peptide 1 receptor gene., *Nat. Med.* **2**, 1254–8 (1996).

36. J. E. Ayala, D. P. Bracy, F. D. James, M. a Burmeister, D. H. Wasserman, D. J. Drucker, Glucagon-like peptide-1 receptor knockout mice are protected from high-fat diet-induced insulin resistance., *Endocrinology* **151**, 4678–87 (2010).

37. R. Seifert, K. Wenzel-Seifert, Constitutive activity of G-protein-coupled receptors: cause of disease and common property of wild-type receptors., *Naunyn. Schmiedeberg's Arch. Pharmacol.* **366**, 381–416 (2002).

38. J. Fortin, J. C. Schroeder, Y. Zhu, M. Beinborn, A. S. Kopin, Pharmacological characterization of human incretin receptor missense variants., *J. Pharmacol. Exp. Ther.* **332**, 274–80 (2010).

39. C. Koole, D. Wootten, J. Simms, C. Valant, L. J. Miller, A. Christopoulos, P. M. Sexton, Polymorphism and ligand dependent changes in human glucagon-like peptide-1 receptor (GLP-1R) function: allosteric rescue of loss of function mutation., *Mol. Pharmacol.* **80**, 486–97 (2011).

40. R. Collins, What makes UK Biobank special?, *Lancet* **379**, 1173–4 (2012).

41. D. J. Drucker, M. a Nauck, The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes., *Lancet* **368**, 1696–705 (2006).

42. M. Firmann, V. Mayor, P. M. Vidal, M. Bochud, A. Pécoud, D. Hayoz, F. Paccaud, M. Preisig, K. S. Song, X. Yuan, T. M. Danoff, H. a Stirnadel, D. Waterworth, V. Mooser, G. Waeber, P. Vollenweider, The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome., *BMC Cardiovasc. Disord.* **8**, 6 (2008).

43. D. F. Wyszynski, D. M. Waterworth, P. J. Barter, J. Cohen, Y. A. Kesäniemi, R. W. Mahley, R. McPherson, G. Waeber, T. P. Bersot, S. S. Sharma, V. Nolan, L. T. Middleton, S. S. Sundseth, L. a Farrer, V. Mooser, S. M. Grundy, Relation between atherogenic dyslipidemia and the Adult Treatment Program-III definition of metabolic syndrome (Genetic Epidemiology of Metabolic Syndrome Project)., *Am. J. Cardiol.* **95**, 194–8 (2005).

44. N. G. Forouhi, J. Luan, S. Hennings, N. J. Wareham, Incidence of Type 2 diabetes in England and its association with baseline impaired fasting glucose: the Ely study 1990-2000., *Diabet. Med.* **24**, 200–7 (2007).

45. N. Day, S. Oakes, R. Luben, K. T. Khaw, S. Bingham, A. Welch, N. Wareham, EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer., *Br. J. Cancer* **80 Suppl 1**, 95–103 (1999).

46. E. D. L. Rolfe, R. J. F. Loos, C. Druet, R. P. Stolk, U. Ekelund, S. J. Griffin, N. G. Forouhi, N. J. Wareham, K. K. Ong, Association between birth weight and visceral fat in adults., *Am. J. Clin. Nutr.* **92**, 347–52 (2010).

47. J. S. Kooner, J. C. Chambers, C. a Aguilar-Salinas, D. A Hinds, C. L. Hyde, G. R. Warnes, F. J. Gómez Pérez, K. a Frazer, P. Elliott, J. Scott, P. M. Milos, D. R. Cox, J. F. Thompson, Genome-wide scan identifies variation in MLXIPL associated with plasma triglycerides., *Nat. Genet.* **40**, 149–51 (2008).

48. J. B. Echouffo-Tcheugui, R. K. Simmons, K. M. Williams, R. S. Barling, a T. Prevost, A. L. Kinmonth, N. J. Wareham, S. J. Griffin, The ADDITION-Cambridge trial protocol: a cluster -- randomised controlled trial of screening for type 2 diabetes and intensive treatment for screen-detected patients., *BMC Public Health* **9**, 136 (2009).

49. R. Saxena, M.-F. Hivert, C. Langenberg, T. Tanaka, J. S. Pankow, P. Vollenweider, V. Lyssenko, N. Bouatia-Naji, J. Dupuis, A. U. Jackson, W. H. L. Kao, M. Li, N. L. Glazer, A. K. Manning, J. Luan, H. M. Stringham, I. Prokopenko, T. Johnson, N. Grarup, T. W. Boesgaard, C. Lecoeur, P. Shrader, J. O'Connell, E. Ingelsson, D. J. Couper, K. Rice, K. Song, C. H. Andreassen, C. Dina, A. Köttgen, O. Le Bacquer, F. Pattou, J. Taneera, V. Steinthorsdottir, D. Rybin, K. Ardlie, M. Sampson, L. Qi, M. van Hoek, M. N. Weedon, Y. S. Aulchenko, B. F. Voight, H. Grallert, B. Balkau, R. N. Bergman, S. J. Bielinski, A. Bonnefond, L. L. Bonnycastle, K. Borch-Johnsen, Y. Böttcher, E. Brunner, T. a Buchanan, S. J. Bumpstead, C. Cavalcanti-Proença, G. Charpentier, Y.-D. I. Chen, P. S. Chines, F. S. Collins, M. Cornelis, G. J. Crawford, J. Delplanque, A. Doney, J. M. Egan, M. R. Erdos, M. Firmann, N. G. Forouhi, C. S. Fox, M. O. Goodarzi, J. Graessler, A. Hingorani, B. Isomaa, T. Jørgensen, M. Kivimaki, P. Kovacs, K. Krohn, M. Kumari, T. Lauritzen, C. Lévy-Marchal, V. Mayor, J. B. McAteer, D. Meyre, B. D. Mitchell, K. L. Mohlke, M. a Morken, N. Narisu, C. N. a Palmer, R. Pakyz, L. Pascoe, F. Payne, D. Pearson, W. Rathmann, A. Sandbaek, A. A. Sayer, L. J. Scott, S. J. Sharp, E. Sijbrands, A. Singleton, D. S. Siscovick, N. L. Smith, T. Sparsø, A. J. Swift, H. Syddall, G. Thorleifsson, A. Tönjes, T. Tuomi, J. Tuomilehto, T. T. Valle, G. Waeber, A. Walley, D. M. Waterworth, E. Zeggini, J. H. Zhao, T. Illig, H. E. Wichmann, J. F. Wilson, C. van Duijn, F. B. Hu, A. D. Morris, T. M. Frayling, A. T. Hattersley, U. Thorsteinsdottir, K. Stefansson, P. Nilsson, A.-C. Syvänen, A. R. Shuldiner, M. Walker, S. R. Bornstein, P. Schwarz, G. H. Williams, D. M. Nathan, J. Kuusisto, M. Laakso, C. Cooper, M. Marmot, L. Ferrucci, V. Mooser, M. Stumvoll, R. J. F. Loos, D. Altshuler, B. M. Psaty, J. I. Rotter, E. Boerwinkle, T. Hansen, O. Pedersen, J. C. Florez, M. I. McCarthy, M. Boehnke, I. Barroso, R. Sladek, P. Froguel, J. B. Meigs, L. Groop, N. J. Wareham, R. M. Watanabe, Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge., *Nat. Genet.* **42**, 142–8 (2010).

50. R. A. Scott, V. Lagou, R. P. Welch, E. Wheeler, M. E. Montasser, J. Luan, R. Mägi, R. J. Strawbridge, E. Rehnberg, S. Gustafsson, S. Kanoni, L. J. Rasmussen-Torvik, L. Yengo, C. Lecoeur, D. Shungin, S. Sanna, C. Sidore, P. C. D. Johnson, J. W. Jukema, T. Johnson, A. Mahajan, N. Verweij, G. Thorleifsson, J.-J. Hottenga, S. Shah, A. V Smith, B. Sennblad, C. Gieger, P. Salo, M. Perola, N. J. Timpson, D. M. Evans, B. S. Pourcain, Y. Wu, J. S. Andrews, J. Hui, L. F. Bielak, W. Zhao, M. Horikoshi, P. Navarro, A. Isaacs, J. R. O'Connell, K. Stirrups, V. Vitart, C. Hayward, T. Esko, E. Mihailov, R. M. Fraser, T. Fall, B. F. Voight, S. Raychaudhuri, H. Chen, C. M. Lindgren, A. P. Morris, N. W. Rayner, N. Robertson, D. Rybin, C.-T. Liu, J. S. Beckmann, S. M. Willems, P. S. Chines, A. U. Jackson, H. M. Kang, H. M. Stringham, K. Song, T. Tanaka, J. F. Peden, A. Goel, A. a Hicks, P. An, M. Müller-Nurasyid, A. Franco-Cereceda, L. Folkersen, L. Marullo, H. Jansen, A. J. Oldehinkel, M. Bruinenberg, J. S. Pankow, K. E. North, N. G. Forouhi, R. J. F. Loos, S. Edkins, T. V Varga, G. Hallmans, H. Oksa, M. Antonella, R. Nagaraja, S. Trompet, I. Ford, S. J. L. Bakker, A. Kong, M. Kumari, B. Gigante, C. Herder, P. B. Munroe, M. Caulfield, J. Antti, M. Mangino, K. Small, I. Miljkovic, Y. Liu, M. Atalay, W. Kiess, A. L. James, F. Rivadeneira, A. G. Uitterlinden, C. N. a Palmer, A. S. F. Doney, G. Willemsen, J. H. Smit, S. Campbell, O. Polasek, L. L. Bonnycastle, S. Hercberg, M. Dimitriou, J. L. Bolton, G. R. Fowkes, P. Kovacs, J. Lindström, T. Zemunik, S. Bandinelli, S. H. Wild, H. V Basart, W. Rathmann, H. Grallert, W. Maerz, M. E. Kleber, B. O. Boehm, A. Peters, P. P. Pramstaller, M. a Province, I. B. Borecki, N. D. Hastie, I. Rudan, H. Campbell, H. Watkins, M. Farrall, M. Stumvoll, L. Ferrucci, D. M. Waterworth, R. N. Bergman, F. S. Collins, J. Tuomilehto, R. M. Watanabe, E. J. C. de Geus, B. W. Penninx, A. Hofman, B. a Oostra, B. M. Psaty, P. Vollenweider, J. F. Wilson, A. F. Wright, G. K. Hovingh, A. Metspalu, M. Uusitupa, P. K. E. Magnusson, K. O. Kyvik, J. Kaprio, J. F. Price, G. V Dedoussis, P. Deloukas, P. Meneton, L. Lind, M. Boehnke, A. R. Shuldiner, C. M. van Duijn, A. D. Morris, A. Toenjes, P. a Peyser, J. P. Beilby, A. Körner, J. Kuusisto, M. Laakso, S. R. Bornstein, P. E. H. Schwarz, T. a Lakka, R. Rauramaa, L. S. Adair, G. D. Smith, T. D. Spector, T. Illig, U. de Faire, A. Hamsten, V. Gudnason, M. Kivimaki, A. Hingorani, S. M. Keinanen-Kiukaanniemi, T. E. Saaristo, D. I. Boomsma, K. Stefansson, P. van der Harst, J. Dupuis, N. L. Pedersen, N. Sattar, T. B. Harris, F. Cucca, S. Ripatti, V. Salomaa, K. L. Mohlke, B. Balkau, P. Froguel, A. Pouta, M.-R. Jarvelin, N. J. Wareham, N. Bouatia-Naji, M. I. McCarthy, P. W. Franks, J. B. Meigs, T. M. Teslovich, J. C. Florez, C. Langenberg, E. Ingelsson, I. Prokopenko, I. Barroso, Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the

underlying biological pathways., *Nat. Genet.* **44**, 991–1005 (2012).

51. A. K. Manning, M.-F. Hivert, R. A. Scott, J. L. Grimsby, N. Bouatia-Naji, H. Chen, D. Rybin, C.-T. Liu, L. F. Bielak, I. Prokopenko, N. Amin, D. Barnes, G. Cadby, J.-J. Hottenga, E. Ingelsson, A. U. Jackson, T. Johnson, S. Kanoni, C. Ladenvall, V. Lagou, J. Lahti, C. Lecoeur, Y. Liu, M. T. Martinez-Larrad, M. E. Montasser, P. Navarro, J. R. B. Perry, L. J. Rasmussen-Torvik, P. Salo, N. Sattar, D. Shungin, R. J. Strawbridge, T. Tanaka, C. M. van Duijn, P. An, M. de Andrade, J. S. Andrews, T. Aspelund, M. Atalay, Y. Aulchenko, B. Balkau, S. Bandinelli, J. S. Beckmann, J. P. Beilby, C. Bellis, R. N. Bergman, J. Blangero, M. Boban, M. Boehnke, E. Boerwinkle, L. L. Bonnycastle, D. I. Boomsma, I. B. Borecki, Y. Böttcher, C. Bouchard, E. Brunner, D. Budimir, H. Campbell, O. Carlson, P. S. Chines, R. Clarke, F. S. Collins, A. Corbatón-Anchuelo, D. Couper, U. de Faire, G. V Dedoussis, P. Deloukas, M. Dimitriou, J. M. Egan, G. Eiriksdottir, M. R. Erdos, J. G. Eriksson, E. Eury, L. Ferrucci, I. Ford, N. G. Forouhi, C. S. Fox, M. G. Franzosi, P. W. Franks, T. M. Frayling, P. Froguel, P. Galan, E. de Geus, B. Gigante, N. L. Glazer, A. Goel, L. Groop, V. Gudnason, G. Hallmans, A. Hamsten, O. Hansson, T. B. Harris, C. Hayward, S. Heath, S. Hercberg, A. a Hicks, A. Hingorani, A. Hofman, J. Hui, J. Hung, M.-R. Jarvelin, M. a Jhun, P. C. D. Johnson, J. W. Jukema, A. Jula, W. H. Kao, J. Kaprio, S. L. R. Kardia, S. Keinänen-Kiukaanniemi, M. Kivimaki, I. Kolcic, P. Kovacs, M. Kumari, J. Kuusisto, K. O. Kyvik, M. Laakso, T. Lakka, L. Lannfelt, G. M. Lathrop, L. J. Launer, K. Leander, G. Li, L. Lind, J. Lindstrom, S. Lobbens, R. J. F. Loos, J. Luan, V. Lyssenko, R. Mägi, P. K. E. Magnusson, M. Marmot, P. Meneton, K. L. Mohlke, V. Mooser, M. a Morken, I. Miljkovic, N. Narisu, J. O'Connell, K. K. Ong, B. a Oostra, L. J. Palmer, A. Palotie, J. S. Pankow, J. F. Peden, N. L. Pedersen, M. Pehlic, L. Peltonen, B. Penninx, M. Pericic, M. Perola, L. Perusse, P. a Peyser, O. Polasek, P. P. Pramstaller, M. a Province, K. Räikkönen, R. Rauramaa, E. Rehnberg, K. Rice, J. I. Rotter, I. Rudan, A. Ruukonen, T. Saaristo, M. Sabater-Lleal, V. Salomaa, D. B. Savage, R. Saxena, P. Schwarz, U. Seedorf, B. Sennblad, M. Serrano-Rios, A. R. Shuldiner, E. J. G. Sijbrands, D. S. Siscovick, J. H. Smit, K. S. Small, N. L. Smith, A. V. Smith, A. Stančáková, K. Stirrups, M. Stumvoll, Y. V Sun, A. J. Swift, A. Tönjes, J. Tuomilehto, S. Trompet, A. G. Uitterlinden, M. Uusitupa, M. Vikström, V. Vitart, M.-C. Vohl, B. F. Voight, P. Vollenweider, G. Waeber, D. M. Waterworth, H. Watkins, E. Wheeler, E. Widen, S. H. Wild, S. M. Willems, G. Willemssen, J. F. Wilson, J. C. M. Witteman, A. F. Wright, H. Yaghoobkar, D. Zelenika, T. Zemunik, L. Zgaga, N. J. Wareham, M. I. McCarthy, I. Barroso, R. M. Watanabe, J. C. Florez, J. Dupuis, J. B. Meigs, C. Langenberg, A genome-wide approach accounting for body mass index identifies genetic variants influencing fasting glycemic traits and insulin resistance., *Nat. Genet.* **44**, 659–69 (2012).

52. T. Johnson, T. R. Gaunt, S. J. Newhouse, S. Padmanabhan, M. Tomaszewski, M. Kumari, R. W. Morris, I. Tzoulaki, E. T. O'Brien, N. R. Poulter, P. Sever, D. C. Shields, S. Thom, S. G. Wannamethee, P. H. Whincup, M. J. Brown, J. M. Connell, R. J. Dobson, P. J. Howard, C. a Mein, A. Onipinla, S. Shaw-Hawkins, Y. Zhang, G. Davey Smith, I. N. M. Day, D. a Lawlor, A. H. Goodall, F. G. Fowkes, G. R. Abecasis, P. Elliott, V. Gateva, P. S. Braund, P. R. Burton, C. P. Nelson, M. D. Tobin, P. van der Harst, N. Glorioso, H. Neuvirth, E. Salvi, J. a Staessen, A. Stucchi, N. Devos, X. Jeunemaitre, P.-F. Plouin, J. Tichet, P. Juhanson, E. Org, M. Putku, S. Söber, G. Veldre, M. Viigimaa, A. Levinsson, A. Rosengren, D. S. Thelle, C. E. Hastie, T. Hedner, W. K. Lee, O. Melander, B. Wahlstrand, R. Hardy, A. Wong, J. a Cooper, J. Palmen, L. Chen, A. F. R. Stewart, G. a Wells, H.-J. Westra, M. G. M. Wolfs, R. Clarke, M. G. Franzosi, A. Goel, A. Hamsten, M. Lathrop, J. F. Peden, U. Seedorf, H. Watkins, W. H. Ouwehand, J. Sambrook, J. Stephens, J.-P. Casas, F. Drenos, M. V Holmes, M. Kivimaki, S. Shah, T. Shah, P. J. Talmud, J. Whittaker, C. Wallace, C. Delles, M. Laan, D. Kuh, S. E. Humphries, F. Nyberg, D. Cusi, R. Roberts, C. Newton-Cheh, L. Franke, A. V Stanton, A. F. Dominiczak, M. Farrall, A. D. Hingorani, N. J. Samani, M. J. Caulfield, P. B. Munroe, Blood pressure loci identified with a gene-centric array., *Am. J. Hum. Genet.* **89**, 688–700 (2011).

53. M. den Hoed, M. Eijgelsheim, T. Esko, B. J. J. M. Brundel, D. S. Peal, D. M. Evans, I. M. Nolte, A. V Segrè, H. Holm, R. E. Handsaker, H.-J. Westra, T. Johnson, A. Isaacs, J. Yang, A. Lundby, J. H. Zhao, Y. J. Kim, M. J. Go, P. Almgren, M. Bochud, G. Boucher, M. C. Cornelis, D. Gudbjartsson, D. Hadley, P.

van der Harst, C. Hayward, M. den Heijer, W. Igl, A. U. Jackson, Z. Kutalik, J. Luan, J. P. Kemp, K. Kristiansson, C. Ladvall, M. Lorentzon, M. E. Montasser, O. T. Njajou, P. F. O'Reilly, S. Padmanabhan, B. St Pourcain, T. Rankinen, P. Salo, T. Tanaka, N. J. Timpson, V. Vitart, L. Waite, W. Wheeler, W. Zhang, H. H. M. Draisma, M. F. Feitosa, K. F. Kerr, P. a Lind, E. Mihailov, N. C. Onland-Moret, C. Song, M. N. Weedon, W. Xie, L. Yengo, D. Absher, C. M. Albert, A. Alonso, D. E. Arking, P. I. W. de Bakker, B. Balkau, C. Barlassina, P. Benaglio, J. C. Bis, N. Bouatia-Naji, S. Brage, S. J. Chanock, P. S. Chines, M. Chung, D. Darbar, C. Dina, M. Dörr, P. Elliott, S. B. Felix, K. Fischer, C. Fuchsberger, E. J. C. de Geus, P. Goyette, V. Gudnason, T. B. Harris, A.-L. Hartikainen, A. S. Havulinna, S. R. Heckbert, A. a Hicks, A. Hofman, S. Holewijn, F. Hoogstra-Berends, J.-J. Hottenga, M. K. Jensen, A. Johansson, J. Junttila, S. Kääb, B. Kanon, S. Ketkar, K.-T. Khaw, J. W. Knowles, A. S. Kooner, J. a Kors, M. Kumari, L. Milani, P. Laiho, E. G. Lakatta, C. Langenberg, M. Leusink, Y. Liu, R. N. Luben, K. L. Lunetta, S. N. Lynch, M. R. P. Markus, P. Marques-Vidal, I. Mateo Leach, W. L. McArdle, S. a McCarroll, S. E. Medland, K. a Miller, G. W. Montgomery, A. C. Morrison, M. Müller-Nurasyid, P. Navarro, M. Nelis, J. R. O'Connell, C. J. O'Donnell, K. K. Ong, A. B. Newman, A. Peters, O. Polasek, A. Pouta, P. P. Pramstaller, B. M. Psaty, D. C. Rao, S. M. Ring, E. J. Rossin, D. Rudan, S. Sanna, R. a Scott, J. S. Sehmi, S. Sharp, J. T. Shin, A. B. Singleton, A. V Smith, N. Soranzo, T. D. Spector, C. Stewart, H. M. Stringham, K. V Tarasov, A. G. Uitterlinden, L. Vandenput, S.-J. Hwang, J. B. Whitfield, C. Wijmenga, S. H. Wild, G. Willemsen, J. F. Wilson, J. C. M. Witteman, A. Wong, Q. Wong, Y. Jamshidi, P. Zitting, J. M. a Boer, D. I. Boomsma, I. B. Borecki, C. M. van Duijn, U. Ekelund, N. G. Forouhi, P. Froguel, A. Hingorani, E. Ingelsson, M. Kivimäki, R. a Kronmal, D. Kuh, L. Lind, N. G. Martin, B. a Oostra, N. L. Pedersen, T. Quertermous, J. I. Rotter, Y. T. van der Schouw, W. M. M. Verschuren, M. Walker, D. Albanes, D. O. Arnar, T. L. Assimes, S. Bandinelli, M. Boehnke, R. a de Boer, C. Bouchard, W. L. M. Caulfield, J. C. Chambers, G. Curhan, D. Cusi, J. Eriksson, L. Ferrucci, W. H. van Gilst, N. Glorioso, J. de Graaf, L. Groop, U. Gyllenstein, W.-C. Hsueh, F. B. Hu, H. V Huikuri, D. J. Hunter, C. Iribarren, B. Isomaa, M.-R. Jarvelin, A. Jula, M. Kähönen, L. a Kiemeny, M. M. van der Klauw, J. S. Kooner, P. Kraft, L. Iacoviello, T. Lehtimäki, M.-L. L. Lokki, B. D. Mitchell, G. Navis, M. S. Nieminen, C. Ohlsson, N. R. Poulter, L. Qi, O. T. Raitakari, E. B. Rimm, J. D. Rioux, F. Rizzi, I. Rudan, V. Salomaa, P. S. Sever, D. C. Shields, A. R. Shuldiner, J. Sinisalo, A. V Stanton, R. P. Stolk, D. P. Strachan, J.-C. Tardif, U. Thorsteinsdottir, J. Tuomilehto, D. J. van Veldhuisen, J. Virtamo, J. Viikari, P. Vollenweider, G. Waeber, E. Widen, Y. S. Cho, J. V Olsen, P. M. Visscher, C. Willer, L. Franke, J. Erdmann, J. R. Thompson, A. Pfeuffer, N. Sotoodehnia, C. Newton-Cheh, P. T. Ellinor, B. H. C. Stricker, A. Metspalu, M. Perola, J. S. Beckmann, G. D. Smith, K. Stefansson, N. J. Wareham, P. B. Munroe, O. C. M. Sibon, D. J. Milan, H. Snieder, N. J. Samani, R. J. F. Loos, Identification of heart rate-associated loci and their effects on cardiac conduction and rhythm disorders., *Nat. Genet.* **45**, 621–31 (2013).

54. M. D. Mailman, M. Feolo, Y. Jin, M. Kimura, K. Tryka, R. Bagoutdinov, L. Hao, A. Kiang, J. Paschall, L. Phan, N. Popova, S. Pretel, L. Ziyabari, M. Lee, Y. Shao, Z. Y. Wang, K. Sirotkin, M. Ward, M. Kholodov, K. Zbicz, J. Beck, M. Kimelman, S. Shevelev, D. Preuss, E. Yaschenko, A. Graeff, J. Ostell, S. T. Sherry, The NCBI dbGaP database of genotypes and phenotypes., *Nat. Genet.* **39**, 1181–6 (2007).

55. B. M. Wolpin, C. Rizzato, P. Kraft, C. Kooperberg, G. M. Petersen, Z. Wang, A. a Arslan, L. Beane-Freeman, P. M. Bracci, J. Buring, F. Canzian, E. J. Duell, S. Gallinger, G. G. Giles, G. E. Goodman, P. J. Goodman, E. J. Jacobs, A. Kaminen, A. P. Klein, L. N. Kolonel, M. H. Kulke, D. Li, N. Malats, S. H. Olson, H. a Risch, H. D. Sesso, K. Visvanathan, E. White, W. Zheng, C. C. Abnet, D. Albanes, G. Andreotti, M. a Austin, R. Barfield, D. Basso, S. I. Berndt, M.-C. Boutron-Ruault, M. Brotzman, M. W. Buehler, H. B. Bueno-de-Mesquita, P. Bugert, L. Burdette, D. Campa, N. E. Caporaso, G. Capurso, C. Chung, M. Cotterchio, E. Costello, J. Elena, N. Funel, J. M. Gaziano, N. a Giese, E. L. Giovannucci, M. Goggins, M. J. Gorman, M. Gross, C. a Haiman, M. Hassan, K. J. Helzlsouer, B. E. Henderson, E. a Holly, N. Hu, D. J. Hunter, F. Innocenti, M. Jenab, R. Kaaks, T. J. Key, K.-T. Khaw, E. a Klein, M. Kogevinas, V. Krogh, J. Kupcinskis, R. C. Kurtz, A. LaCroix, M. T. Landi, S. Landi, L. Le Marchand, A. Mambrini, S. Mannisto, R. L. Milne, Y. Nakamura, A. L. Oberg, K. Owzar, A. V Patel, P. H. M. Peeters, U. Peters, R. Pezzilli, A. Piepoli, M. Porta, F. X. Real, E. Riboli, N. Rothman, A. Scarpa, X.-O. Shu, D. T.

- Silverman, P. Soucek, M. Sund, R. Talar-Wojnarowska, P. R. Taylor, G. E. Theodoropoulos, M. Thornquist, A. Tjønneland, G. S. Tobias, D. Trichopoulos, P. Vodicka, J. Wactawski-Wende, N. Wentzensen, C. Wu, H. Yu, K. Yu, A. Zeleniuch-Jacquotte, R. Hoover, P. Hartge, C. Fuchs, S. J. Chanock, R. S. Stolzenberg-Solomon, L. T. Amundadottir, Genome-wide association study identifies multiple susceptibility loci for pancreatic cancer., *Nat. Genet.* **46**, 994–1000 (2014).
56. M. A. Nalls, N. Pankratz, C. M. Lill, C. B. Do, D. G. Hernandez, M. Saad, A. L. DeStefano, E. Kara, J. Bras, M. Sharma, C. Schulte, M. F. Keller, S. Arepalli, C. Letson, C. Edsall, H. Stefansson, X. Liu, H. Pliner, J. H. Lee, R. Cheng, M. A. Ikram, J. P. A. Ioannidis, G. M. Hadjigeorgiou, J. C. Bis, M. Martinez, J. S. Perlmutter, A. Goate, K. Marder, B. Fiske, M. Sutherland, G. Xiromerisiou, R. H. Myers, L. N. Clark, K. Stefansson, J. A. Hardy, P. Heutink, H. Chen, N. W. Wood, H. Houlden, H. Payami, A. Brice, W. K. Scott, T. Gasser, L. Bertram, N. Eriksson, T. Foroud, A. B. Singleton, Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease., *Nat. Genet.* **056**, 1–7 (2014).
57. J. Zhang, H. Kesteloot, Anthropometric, lifestyle and metabolic determinants of resting heart rate. A population study., *Eur. Heart J.* **20**, 103–10 (1999).
58. J. Gauderman, D. Ph, J. Morrison, QUANTO 1.1: A computer program for power and sample size calculations for genetic-epidemiology studies, <http://hydra.usc.edu/gxe> , 35–50 (2006).
59. N. Sarwar, P. Gao, S. R. K. Seshasai, R. Gobin, S. Kaptoge, E. Di Angelantonio, E. Ingelsson, D. a Lawlor, E. Selvin, M. Stampfer, C. D. a Stehouwer, S. Lewington, L. Pennells, a Thompson, N. Sattar, I. R. White, K. K. Ray, J. Danesh, Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies., *Lancet* **375**, 2215–22 (2010).
60. N. G. Forouhi, Z. Ye, A. P. Rickard, K. T. Khaw, R. Luben, C. Langenberg, N. J. Wareham, Circulating 25-hydroxyvitamin D concentration and the risk of type 2 diabetes: results from the European Prospective Investigation into Cancer (EPIC)-Norfolk cohort and updated meta-analysis of prospective studies., *Diabetologia* **55**, 2173–82 (2012).
61. M. M. Swarbrick, B. Waldenmaier, L. a Pennacchio, D. L. Lind, M. M. Cavazos, F. Geller, R. Merriman, A. Ustaszewska, M. Malloy, A. Scherag, W.-C. Hsueh, W. Rief, F. Mauvais-Jarvis, C. R. Pullinger, J. P. Kane, R. Dent, R. McPherson, P.-Y. Kwok, A. Hinney, J. Hebebrand, C. Vaisse, Lack of support for the association between GAD2 polymorphisms and severe human obesity., *PLoS Biol.* **3**, e315 (2005).
62. C. Langenberg, S. Sharp, N. G. Forouhi, P. W. Franks, M. B. Schulze, N. Kerrison, U. Ekelund, I. Barroso, S. Panico, M. J. Tormo, J. Spranger, S. Griffin, Y. T. van der Schouw, P. Amiano, E. Ardanaz, L. Arriola, B. Balkau, a Barricarte, J. W. J. Beulens, H. Boeing, H. B. Bueno-de-Mesquita, B. Buijsse, M. D. Chirlaque Lopez, F. Clavel-Chapelon, F. L. Crowe, B. de Lauzon-Guillan, P. Deloukas, M. Dorronsoro, D. Drogan, P. Froguel, C. Gonzalez, S. Grioni, L. Groop, C. Groves, P. Hainaut, J. Halkjaer, G. Hallmans, T. Hansen, J. M. Huerta Castaño, R. Kaaks, T. J. Key, K. T. Khaw, a Koulman, a Mattiello, C. Navarro, P. Nilsson, T. Norat, K. Overvad, L. Palla, D. Palli, O. Pedersen, P. H. Peeters, J. R. Quirós, a Ramachandran, L. Rodriguez-Suarez, O. Rolandsson, D. Romaguera, I. Romieu, C. Sacerdote, M. J. Sánchez, a Sandbaek, N. Slimani, I. Sluijs, a M. W. Spijkerman, B. Teucher, a Tjønneland, R. Tumino, D. L. van der A, W. M. M. Verschuren, J. Tuomilehto, E. Feskens, M. McCarthy, E. Riboli, N. J. Wareham, Design and cohort description of the InterAct Project: an examination of the interaction of genetic and lifestyle factors on the incidence of type 2 diabetes in the EPIC Study., *Diabetologia* **54**, 2272–82 (2011).
63. E. Riboli, K. J. Hunt, N. Slimani, P. Ferrari, T. Norat, M. Fahey, U. R. Charrondière, B. Hémon, C. Casagrande, J. Vignat, K. Overvad, a Tjønneland, F. Clavel-Chapelon, a Thiébaud, J. Wahrendorf, H.

- Boeing, D. Trichopoulos, a Trichopoulou, P. Vineis, D. Palli, H. B. Bueno-De-Mesquita, P. H. M. Peeters, E. Lund, D. Engeset, C. a González, a Barricarte, G. Berglund, G. Hallmans, N. E. Day, T. J. Key, R. Kaaks, R. Saracci, European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection., *Public Health Nutr.* **5**, 1113–24 (2002).
64. B. G. Nordestgaard, M. Benn, P. Schnohr, A. Tybjaerg-Hansen, Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women., *JAMA* **298**, 299–308 (2007).
65. J. Danesh, R. Saracci, G. Berglund, E. Feskens, K. Overvad, S. Panico, S. Thompson, A. Fournier, F. Clavel-Chapelon, M. Canonico, R. Kaaks, J. Linseisen, H. Boeing, T. Pischon, C. Weikert, A. Olsen, A. Tjønneland, S. P. Johnsen, M. K. Jensen, J. R. Quirós, C. A. G. Svatetz, M.-J. S. Pérez, N. Larrañaga, C. N. Sanchez, C. M. Iribas, S. Bingham, K.-T. Khaw, N. Wareham, T. Key, A. Roddam, A. Trichopoulou, V. Benetou, D. Trichopoulos, G. Masala, S. Sieri, R. Tumino, C. Sacerdote, A. Mattiello, W. M. M. Verschuren, H. B. Bueno-de-Mesquita, D. E. Grobbee, Y. T. van der Schouw, O. Melander, G. Hallmans, P. Wennberg, E. Lund, M. Kumle, G. Skeie, P. Ferrari, N. Slimani, T. Norat, E. Riboli, EPIC-Heart: the cardiovascular component of a prospective study of nutritional, lifestyle and biological factors in 520,000 middle-aged participants from 10 European countries., *Eur. J. Epidemiol.* **22**, 129–41 (2007).
66. S. Bingham, E. Riboli, Diet and cancer--the European Prospective Investigation into Cancer and Nutrition., *Nat. Rev. Cancer* **4**, 206–15 (2004).
67. J. Shepherd, S. M. Cobbe, I. Ford, C. G. Isles, A. R. Lorimer, P. W. MacFarlane, J. H. McKillop, C. J. Packard, Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group., *N. Engl. J. Med.* **333**, 1301–7 (1995).
68. J. Shepherd, G. J. Blauw, M. B. Murphy, E. L. E. M. Bollen, B. M. Buckley, S. M. Cobbe, I. Ford, A. Gaw, M. Hyland, J. W. Jukema, A. M. Kamper, P. W. Macfarlane, A. E. Meinders, J. Norrie, C. J. Packard, I. J. Perry, D. J. Stott, B. J. Sweeney, C. Twomey, R. G. J. Westendorp, Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial., *Lancet* **360**, 1623–30 (2002).
69. A. Evans, V. Salomaa, S. Kulathinal, K. Asplund, F. Cambien, M. Ferrario, M. Perola, L. Peltonen, D. Shields, H. Tunstall-Pedoe, K. Kuulasmaa, MORGAM (an international pooling of cardiovascular cohorts)., *Int. J. Epidemiol.* **34**, 21–7 (2005).
70. S. Kulathinal, J. Karvanen, O. Saarela, K. Kuulasmaa, Case-cohort design in practice - experiences from the MORGAM Project., *Epidemiol. Perspect. Innov.* **4**, 15 (2007).
71. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators., *Am. J. Epidemiol.* **129**, 687–702 (1989).
72. T. L. Assimes, H. Hólm, S. Kathiresan, M. P. Reilly, G. Thorleifsson, B. F. Voight, J. Erdmann, C. Willenborg, D. Vaidya, C. Xie, C. C. Patterson, T. M. Morgan, M. S. Burnett, M. Li, M. A. Hlatky, J. W. Knowles, J. R. Thompson, D. Absher, C. Iribarren, A. Go, S. P. Fortmann, S. Sidney, N. Risch, H. Tang, R. M. Myers, K. Berger, M. Stoll, S. H. Shah, G. Thorgeirsson, K. Andersen, A. S. Havulinna, J. E. Herrera, N. Faraday, Y. Kim, B. G. Kral, R. A. Mathias, I. Ruczinski, B. Suktitipat, A. F. Wilson, L. R. Yanek, L. C. Becker, P. Linsel-Nitschke, W. Lieb, I. R. König, C. Hengstenberg, M. Fischer, K. Stark, W. Reinhard, J. Winogradow, M. Grassl, A. Grosshennig, M. Preuss, S. Schreiber, H.-E. Wichmann, C. Meisinger, J. Yee, Y. Friedlander, R. Do, J. B. Meigs, G. Williams, D. M. Nathan, C. A. MacRae, L. Qu, R. L. Wilensky, W. H. Matthai, A. N. Qasim, H. Hakonarson, A. D. Pichard, K. M. Kent, L. Satler, J. M. Lindsay, R. Waksman, C. W. Knouff, D. M. Waterworth, M. C. Walker, V. E. Mooser, J. Marrugat, G. Lucas, I. Subirana, J. Sala, R. Ramos, N. Martinelli, O. Olivieri, E. Trabetti, G. Malerba, P. F. Pignatti, C.

Guiducci, D. Mirel, M. Parkin, J. N. Hirschhorn, R. Asselta, S. Duga, K. Musunuru, M. J. Daly, S. Purcell, S. Eifert, P. S. Braund, B. J. Wright, A. J. Balmforth, S. G. Ball, W. H. Ouwehand, P. Deloukas, M. Scholz, F. Cambien, A. Hugen, T. Scheffold, V. Salomaa, D. Girelli, C. B. Granger, L. Peltonen, P. P. McKeown, D. Altshuler, O. Melander, J. M. Devaney, S. E. Epstein, D. J. Rader, R. Elosua, J. C. Engert, S. S. Anand, A. S. Hall, A. Ziegler, C. J. O'Donnell, J. A. Spertus, D. Siscovick, S. M. Schwartz, D. Becker, U. Thorsteinsdottir, K. Stefansson, H. Schunkert, N. J. Samani, T. Quertermous, Lack of association between the Trp719Arg polymorphism in kinesin-like protein-6 and coronary artery disease in 19 case-control studies., *J. Am. Coll. Cardiol.* **56**, 1552–63 (2010).

73. G. Hallmans, A. Agren, G. Johansson, A. Johansson, B. Stegmayr, J.-H. Jansson, B. Lindahl, O. Rolandsson, S. Söderberg, M. Nilsson, I. Johansson, L. Weinehall, Cardiovascular disease and diabetes in the Northern Sweden Health and Disease Study Cohort - evaluation of risk factors and their interactions., *Scand. J. Public Health. Suppl.* **61**, 18–24 (2003).

74. W. B. Kannel, T. R. Dawber, A. Kagan, N. Revotskie, J. Stokes, Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study., *Ann. Intern. Med.* **55**, 33–50 (1961).

75. S. A. Hills, B. Balkau, S. W. Coppock, J. M. Dekker, A. Mari, A. Natali, M. Walker, E. Ferrannini, The EGIR-RISC STUDY (The European group for the study of insulin resistance: relationship between insulin sensitivity and cardiovascular disease risk): I. Methodology and objectives., *Diabetologia* **47**, 566–70 (2004).

76. M. E. J. Lean, R. Carraro, N. Finan, H. Hartvig, M. L. Lindegaard, S. Rössner, L. Van Gaal, A. Astrup, NN8022-1807 Investigators, Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults., *Int. J. Obes. (Lond).* **38**, 689–97 (2014).

77. A. S. Kelly, K. D. Rudser, B. M. Nathan, C. K. Fox, A. M. Metzger, B. J. Coombes, A. K. Fitch, E. M. Bomberg, M. J. Abuzzahab, The effect of glucagon-like peptide-1 receptor agonist therapy on body mass index in adolescents with severe obesity: a randomized, placebo-controlled, clinical trial., *JAMA Pediatr.* **167**, 355–60 (2013).

78. J. Rosenstock, L. J. Klaff, S. Schwartz, J. Northrup, J. H. Holcombe, K. Wilhelm, M. Trautmann, Effects of exenatide and lifestyle modification on body weight and glucose tolerance in obese subjects with and without pre-diabetes., *Diabetes Care* **33**, 1173–5 (2010).

79. K. Elkind-Hirsch, O. Marrioneaux, M. Bhushan, D. Vernor, R. Bhushan, Comparison of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome., *J. Clin. Endocrinol. Metab.* **93**, 2670–8 (2008).

80. I. Aviles-Olmos, J. Dickson, Z. Kefalopoulou, A. Djamshidian, P. Ell, T. Soderlund, P. Whitton, R. Wyse, T. Isaacs, A. Lees, P. Limousin, T. Foltynie, Exenatide and the treatment of patients with Parkinson's disease., *J. Clin. Invest.* **123**, 2730–6 (2013).

81. S. Madsbad, O. Schmitz, J. Rastam, G. Jakobsen, D. R. Matthews, NN2211-1310 International Study Group, Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial., *Diabetes Care* **27**, 1335–42 (2004).

82. Y. Seino, M. F. Rasmussen, M. Zdravkovic, K. Kaku, Dose-dependent improvement in glycemia with once-daily liraglutide without hypoglycemia or weight gain: A double-blind, randomized, controlled trial in Japanese patients with type 2 diabetes., *Diabetes Res. Clin. Pract.* **81**, 161–8 (2008).

83. M. Marre, J. Shaw, M. Brändle, W. M. W. Bebakar, N. A. Kamaruddin, J. Strand, M. Zdravkovic, T. D. Le Thi, S. Colagiuri, LEAD-1 SU study group, Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU), *Diabet. Med.* **26**, 268–78 (2009).
84. M. Nauck, A. Frid, K. Hermansen, N. S. Shah, T. Tankova, I. H. Mitha, M. Zdravkovic, M. Düring, D. R. Matthews, LEAD-2 Study Group, Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study., *Diabetes Care* **32**, 84–90 (2009).
85. T. Forst, G. Michelson, F. Ratter, M. M. Weber, S. Anders, M. Mitry, B. Wilhelm, A. Pfützner, Addition of liraglutide in patients with Type 2 diabetes well controlled on metformin monotherapy improves several markers of vascular function., *Diabet. Med.* **29**, 1115–8 (2012).
86. B. Zinman, J. Gerich, J. B. Buse, A. Lewin, S. Schwartz, P. Raskin, P. M. Hale, M. Zdravkovic, L. Blonde, LEAD-4 Study Investigators, Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD), *Diabetes Care* **32**, 1224–30 (2009).
87. D. Russell-Jones, A. Vaag, O. Schmitz, B. K. Sethi, N. Lalic, S. Antic, M. Zdravkovic, G. M. Ravn, R. Simó, Liraglutide Effect and Action in Diabetes 5 (LEAD-5) met+SU Study Group, Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial., *Diabetologia* **52**, 2046–55 (2009).
88. D. Kim, L. MacConell, D. Zhuang, P. A. Kothare, M. Trautmann, M. Fineman, K. Taylor, Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes., *Diabetes Care* **30**, 1487–93 (2007).
89. T. Kadowaki, M. Namba, A. Yamamura, H. Sowa, A. M. Wolka, R. G. Brodows, Exenatide exhibits dose-dependent effects on glycemic control over 12 weeks in Japanese patients with suboptimally controlled type 2 diabetes., *Endocr. J.* **56**, 415–24 (2009).
90. T. J. Moretto, D. R. Milton, T. D. Ridge, L. A. Macconell, T. Okerson, A. M. Wolka, R. G. Brodows, Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naïve patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study., *Clin. Ther.* **30**, 1448–60 (2008).
91. D. M. Kendall, M. C. Riddle, J. Rosenstock, D. Zhuang, D. D. Kim, M. S. Fineman, A. D. Baron, Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea., *Diabetes Care* **28**, 1083–91 (2005).
92. R. A. DeFronzo, R. E. Ratner, J. Han, D. D. Kim, M. S. Fineman, A. D. Baron, Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes., *Diabetes Care* **28**, 1092–100 (2005).
93. J. B. Buse, R. R. Henry, J. Han, D. D. Kim, M. S. Fineman, A. D. Baron, Exenatide-113 Clinical Study Group, Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes., *Diabetes Care* **27**, 2628–35 (2004).
94. C. M. Apovian, R. M. Bergenstal, R. M. Cuddihy, Y. Qu, S. Lenox, M. S. Lewis, L. C. Glass, Effects of exenatide combined with lifestyle modification in patients with type 2 diabetes., *Am. J. Med.* **123**, 468.e9–17 (2010).
95. J. B. Buse, R. M. Bergenstal, L. C. Glass, C. R. Heilmann, M. S. Lewis, A. Y. M. Kwan, B. J. Hoogwerf,

- J. Rosenstock, Use of twice-daily exenatide in Basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial., *Ann. Intern. Med.* **154**, 103–12 (2011).
96. A. Gill, B. J. Hoogwerf, J. Burger, S. Bruce, L. Macconell, P. Yan, D. Braun, J. Giaconia, J. Malone, Effect of exenatide on heart rate and blood pressure in subjects with type 2 diabetes mellitus: a double-blind, placebo-controlled, randomized pilot study., *Cardiovasc. Diabetol.* **9**, 6 (2010).
97. J. Liutkus, J. Rosas Guzman, P. Norwood, L. Pop, J. Northrup, D. Cao, M. Trautmann, A placebo-controlled trial of exenatide twice-daily added to thiazolidinediones alone or in combination with metformin., *Diabetes. Obes. Metab.* **12**, 1058–65 (2010).
98. B. Zinman, B. J. Hoogwerf, S. Durán García, D. R. Milton, J. M. Giaconia, D. D. Kim, M. E. Trautmann, R. G. Brodows, The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial., *Ann. Intern. Med.* **146**, 477–85 (2007).
99. R. A. DeFronzo, C. Triplitt, Y. Qu, M. S. Lewis, D. Maggs, L. C. Glass, Effects of exenatide plus rosiglitazone on beta-cell function and insulin sensitivity in subjects with type 2 diabetes on metformin., *Diabetes Care* **33**, 951–7 (2010).
100. G. Derosa, I. G. Franzetti, F. Querci, A. Carbone, L. Ciccarelli, M. N. Piccinni, E. Fogari, P. Maffioli, Exenatide plus metformin compared with metformin alone on β -cell function in patients with Type 2 diabetes., *Diabet. Med.* **29**, 1515–23 (2012).
101. G. Derosa, I. G. Franzetti, F. Querci, A. Carbone, L. Ciccarelli, M. N. Piccinni, E. Fogari, P. Maffioli, Variation in inflammatory markers and glycemic parameters after 12 months of exenatide plus metformin treatment compared with metformin alone: a randomized placebo-controlled trial., *Pharmacotherapy* **33**, 817–26 (2013).
102. Y. Gao, K. H. Yoon, L.-M. Chuang, V. Mohan, G. Ning, S. Shah, H. C. Jang, T.-J. Wu, D. Johns, J. Northrup, R. Brodows, Efficacy and safety of exenatide in patients of Asian descent with type 2 diabetes inadequately controlled with metformin or metformin and a sulphonylurea., *Diabetes Res. Clin. Pract.* **83**, 69–76 (2009).
103. Y. Seino, A. Takami, G. Boka, E. Niemoeller, D. Raccach, PDY6797 investigators, Pharmacodynamics of the glucagon-like peptide-1 receptor agonist lixisenatide in Japanese and Caucasian patients with type 2 diabetes mellitus poorly controlled on sulphonylureas with/without metformin., *Diabetes. Obes. Metab.* **16**, 739–47 (2014).
104. R. E. Ratner, J. Rosenstock, G. Boka, DRI6012 Study Investigators, Dose-dependent effects of the once-daily GLP-1 receptor agonist lixisenatide in patients with Type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled trial., *Diabet. Med.* **27**, 1024–32 (2010).
105. G. B. Bolli, M. Munteanu, S. Dotsenko, E. Niemoeller, G. Boka, Y. Wu, M. Hanefeld, Efficacy and safety of lixisenatide once daily vs. placebo in people with Type 2 diabetes insufficiently controlled on metformin (GetGoal-F1)., *Diabet. Med.* **31**, 176–84 (2014).
106. M. Pinget, R. Goldenberg, E. Niemoeller, I. Muehlen-Bartmer, H. Guo, R. Aronson, Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P)., *Diabetes. Obes. Metab.* **15**, 1000–7 (2013).
107. M. C. Riddle, R. Aronson, P. Home, M. Marre, E. Niemoeller, P. Miossec, L. Ping, J. Ye, J. Rosenstock, Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L)., *Diabetes Care* **36**, 2489–96 (2013).

108. M. C. Riddle, T. Forst, R. Aronson, L. Sauque-Reyna, E. Souhami, L. Silvestre, L. Ping, J. Rosenstock, Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1)., *Diabetes Care* **36**, 2497–503 (2013).
109. B. Ahrén, A. Leguizamo Dimas, P. Miossec, S. Saubadu, R. Aronson, Efficacy and safety of lixisenatide once-daily morning or evening injections in type 2 diabetes inadequately controlled on metformin (GetGoal-M)., *Diabetes Care* **36**, 2543–50 (2013).
110. J. Rosenstock, M. Hanefeld, P. Shamanna, K. W. Min, G. Boka, P. Miossec, T. Zhou, I. Muehlen-Bartmer, R. E. Ratner, Beneficial effects of once-daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin (GetGoal-S)., *J. Diabetes Complications* **28**, 386–92.
111. Y. Seino, K. W. Min, E. Niemoeller, A. Takami, EFC10887 GETGOAL-L Asia Study Investigators, Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia)., *Diabetes. Obes. Metab.* **14**, 910–7 (2012).
112. C. Yu Pan, P. Han, X. Liu, S. Yan, P. Feng, Z. Zhou, X. Lv, H. Tian, Y. Jin Kui, B. Su, S. Shang, E. Niemoeller, Lixisenatide treatment improves glycaemic control in Asian patients with type 2 diabetes mellitus inadequately controlled on metformin with or without sulfonylurea: a randomized, double-blind, placebo-controlled, 24-week trial (GetGoal-M-Asia)., *Diabetes. Metab. Res. Rev.* **30**, 726–35 (2014).
113. V. A. Fonseca, R. Alvarado-Ruiz, D. Raccah, G. Boka, P. Miossec, J. E. Gerich, EFC6018 GetGoal-Mono Study Investigators, Efficacy and safety of the once-daily GLP-1 receptor agonist lixisenatide in monotherapy: a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes (GetGoal-Mono)., *Diabetes Care* **35**, 1225–31 (2012).
114. A. P. Morris, B. F. Voight, T. M. Teslovich, T. Ferreira, A. V Segrè, V. Steinthorsdottir, R. J. Strawbridge, H. Khan, H. Grallert, A. Mahajan, I. Prokopenko, H. M. Kang, C. Dina, T. Esko, R. M. Fraser, S. Kanoni, A. Kumar, V. Lagou, C. Langenberg, J. Luan, C. M. Lindgren, M. Müller-Nurasyid, S. Pechlivanis, N. W. Rayner, L. J. Scott, S. Wiltshire, L. Yengo, L. Kinnunen, E. J. Rossin, S. Raychaudhuri, A. D. Johnson, A. S. Dimas, R. J. F. Loos, S. Vedantam, H. Chen, J. C. Florez, C. Fox, C.-T. Liu, D. Rybin, D. J. Couper, W. H. L. Kao, M. Li, M. C. Cornelis, P. Kraft, Q. Sun, R. M. van Dam, H. M. Stringham, P. S. Chines, K. Fischer, P. Fontanillas, O. L. Holmen, S. E. Hunt, A. U. Jackson, A. Kong, R. Lawrence, J. Meyer, J. R. B. Perry, C. G. P. Platou, S. Potter, E. Rehnberg, N. Robertson, S. Sivapalaratnam, A. Stančáková, K. Stirrups, G. Thorleifsson, E. Tikkanen, A. R. Wood, P. Almgren, M. Atalay, R. Benediktsson, L. L. Bonnycastle, N. Burt, J. Carey, G. Charpentier, A. T. Crenshaw, A. S. F. Doney, M. Dorkhan, S. Edkins, V. Emilsson, E. Eury, T. Forsen, K. Gertow, B. Gigante, G. B. Grant, C. J. Groves, C. Guiducci, C. Herder, A. B. Hreidarsson, J. Hui, A. James, A. Jonsson, W. Rathmann, N. Klopp, J. Kravic, K. Krjutškov, C. Langford, K. Leander, E. Lindholm, S. Lobbens, S. Männistö, G. Mirza, T. W. Mühleisen, B. Musk, M. Parkin, L. Rallidis, J. Saramies, B. Sennblad, S. Shah, G. Sigurðsson, A. Silveira, G. Steinbach, B. Thorand, J. Trakalo, F. Veglia, R. Wennauer, W. Winckler, D. Zabaneh, H. Campbell, C. van Duijn, A. G. Uitterlinden, A. Hofman, E. Sijbrands, G. R. Abecasis, K. R. Owen, E. Zeggini, M. D. Trip, N. G. Forouhi, A.-C. Syvänen, J. G. Eriksson, L. Peltonen, M. M. Nöthen, B. Balkau, C. N. a Palmer, V. Lyssenko, T. Tuomi, B. Isomaa, D. J. Hunter, L. Qi, A. R. Shuldiner, M. Roden, I. Barroso, T. Wilsgaard, J. Beilby, K. Hovingh, J. F. Price, J. F. Wilson, R. Rauramaa, T. a Lakka, L. Lind, G. Dedoussis, I. Njølstad, N. L. Pedersen, K.-T. Khaw, N. J. Wareham, S. M. Keinänen-Kiukaanniemi, T. E. Saaristo, E. Korpi-Hyövälti, J. Saltevo, M. Laakso, J. Kuusisto, A. Metspalu, F. S. Collins, K. L. Mohlke, R. N. Bergman, J. Tuomilehto, B. O. Boehm, C. Gieger, K. Hveem, S. Cauchi, P. Froguel, D. Baldassarre, E. Tremoli, S. E. Humphries, D. Saleheen, J. Danesh, E. Ingelsson, S. Ripatti, V. Salomaa, R. Erbel, K.-H.

Jöckel, S. Moebus, A. Peters, T. Illig, U. de Faire, A. Hamsten, P. J. Donnelly, T. M. Frayling, A. T. Hattersley, E. Boerwinkle, O. Melander, S. Kathiresan, P. M. Nilsson, P. Deloukas, U. Thorsteinsdottir, L. C. Groop, K. Stefansson, F. Hu, J. S. Pankow, J. Dupuis, J. B. Meigs, D. Altshuler, M. Boehnke, M. I. McCarthy, Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes., *Nat. Genet.* **44**, 981–90 (2012).

115. M. Lorenz, C. Pfeiffer, A. Steinsträsser, R. H. A. Becker, H. Rütten, P. Ruus, M. Horowitz, Effects of lixisenatide once daily on gastric emptying in type 2 diabetes--relationship to postprandial glycemia., *Regul. Pept.* **185**, 1–8 (2013).

Acknowledgments: We are grateful for the contributions of the studies and consortia which provided summary results. For a complete list of Acknowledgements, see Supplementary Materials.

Funding: The work described in this manuscript was funded, in part, by GSK, and, in part, by the Medical Research Council (MC_UU_12015/1). CHARGE AD analyses were funded by R01 AG033193 (PI Seshadri). ADGC AD analyses were funded by U01AG032984 (PI Schellenberg). Additional funding sources are outlined in the Supplementary Materials. **Author contributions:** RAS, MGE, NJW, DMW conceived and designed the study. RAS, DFF, LL, AYC, PS, RY, NG, AS, YC, TVV, HY, JAL, JHZ, SMW, JW, SW, NM, KM, AP, SJvdL, CG, AAAO, PA, LA, DA, IAO, BB, AB, IB, SBG, JCB, SB, MB, HB, EB, IBB, JBJ, SB, CC, MC, LAC, CC, JC, MdH, JAD, HME, GBE, EF, JF, TF, IF, NGF, FG, CG, SG, LH, JHJ, MEJ, JWJ, RK, FK, NDK, TJK, JK, ZKJ, ATK, KK, JK, AL, CL, GM, KLM, APM, KM, MMN, PBM, CN, SFN, PMN, BGN, CJP, DP, SP, GMP, MP, AP, CJP, JRQ, OR, CS, VS, MJS, NS, SJS, RS, NS, JAS, DJT, ST, RT, DLvdA, YTvdS, JV, MW, KW, JEA, LTA, JLA, ASB, JC, JD, DFE, RAE, JE, PWF, TMF, TH, JMMH, TJ, JK, ML, CL, MIM, JSP, OP, ER, JIR, DS, NJS, HS, PV, SOR, PD, JD, MOG, SK, JBM, MGE, NJW, DMW participated in the acquisition and/or analysis of data. LL, PS, JAL, JHZ, SJS and JMMH performed analyses and/or provided statistical guidance. IB, SB, MB, HB, EB, IBB, LAC, KLM, PBM, SJS, MW, LTA, JD, DFE, ML, CL, MIM, JSP, PV, SOR, PD, JD, MOG, SK, JBM, MGE, NJW, DMW supervised analyses. RAS, DFF, LL, MGE, NJW, DMW wrote the manuscript, with input from all authors. **Competing interests:** J.L. A, M.G. E, L. L, and D.M. W are GSK stockholders. All named authors are solely responsible for the content of the manuscript. The current manuscript was a collaborative effort between academic and GSK scientists and analyses focused on a subset of genes included in the original sequencing paper (8), which focused on target genes of interest to GlaxoSmithKline. Since October 2015, D.F. has been a full time employee of Bayer AG, Germany. **Data and materials availability:** Data on glycemic traits were contributed by MAGIC investigators and were downloaded from www.magicinvestigators.org. Associations with T2D in a GWAS of Europeans were obtained from The DIAGRAM (DIAbetes Genetics Replication And Meta-analysis) investigators (<http://diagram-consortium.org/downloads.html>). The authors would like to thank the Exome Aggregation Consortium and the groups that provided exome variant data for comparison. A full list of contributing groups can be found at <http://exac.broadinstitute.org/about>. Additional materials can be obtained by request to the corresponding authors and may be subject to MTA requirements.